KISTER

THE LIVING UNIVERSE

An Encyclopaedia of
the Biological Sciences

# The human machine
## *mechanisms*

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# The human machine

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THE LIVING UNIVERSE : AN ENCYCLOPAEDIA OF THE BIOLOGICAL SCIENCES

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*An Encyclopaedia of the Biological Sciences*

S.C.E.R.T., West Bengal
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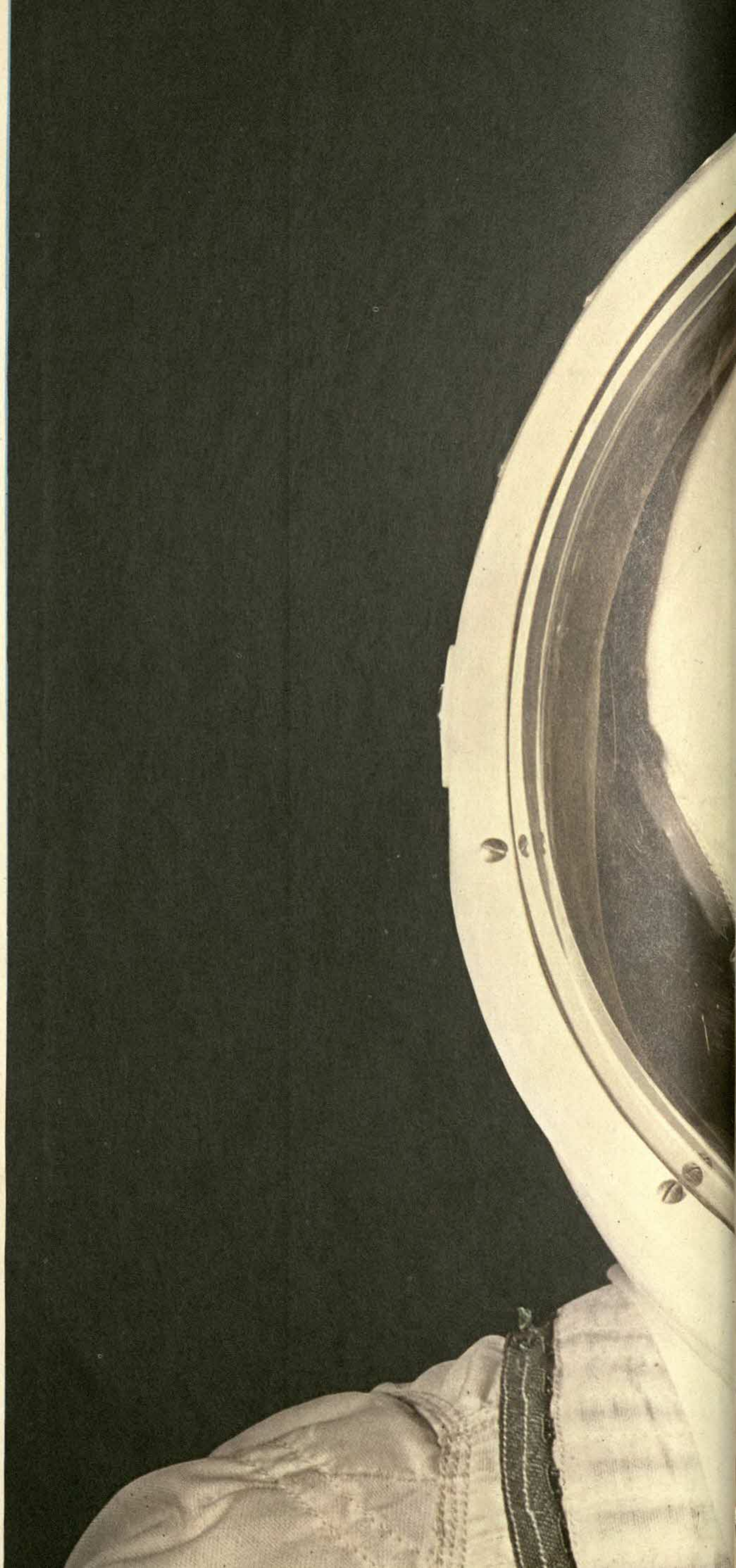
# The human machine

## *mechanisms*

NELSON

*It is in extreme situations that the flexibility and resistance of the human machine are most clearly shown. This astronaut in his space-suit provides the most striking example of the venturesome experiments now being carried out on man. Since life appeared on the surface of the earth and since the living world has been under human control, no organism has ever been subjected to the abnormal conditions of temperature, acceleration and weightlessness which an astronaut must face in an interplanetary rocket. There is no more searching test of the perfection of the human body in adapting itself to conflicting environments and resisting ordeals which its constitution would not appear to be capable of enduring. With its trillions of highly specialized cells and its billions of neurones constituting a nervous system endowed with capacities that are almost boundless, the human machine represents the highest stage of evolution reached by living matter, the supreme subject of study of biological science.*



# THE LIVING UNIVERSE

## *An Encyclopaedia of the Biological Sciences*

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# The human machine: *mechanisms*

*This volume of* THE LIVING UNIVERSE, *An Encyclopaedia of the Biological Sciences, has been produced under the direction of* Alexandre MONNIER *and* Paul LAGET, *in collaboration with* Michel ALBEAUX-FERNET, *Professor of the College of Medicine, Paris, and consultant to the Hospitals of Paris;* Marcel BESSIS, *Director of the Research Laboratories of the National Centre of Blood Transfusion, Paris;* Vincent BLOCH, *Director of Studies at the Sorbonne, Paris;* François BOURLIÈRE, *Professor in the Faculty of Medicine, Paris;* Pierre BUGARD, *D.M., D-ès-Sc., attached to the Hôpital Laennec, Paris;* Michel BURGEAT, *Director of Studies in experimental oto-neurology in the Faculty of Medicine, Paris;* Marc CANTIN, *M.D., Institute of Medicine and Experimental Surgery, University of Montreal, Canada;* Albert DELAUNAY, *Head of the Department of Experimental Pathology at the Institut Pasteur, Garches;* Sir John ECCLES, *F.R.S., President of the National Academy of Sciences of Australia, Director of the Department of Physiology, John Curtin School of Medical Research, Canberra, Australia;* Ragnar GRANIT, *M.D., For.Mem.R.S., formerly Professor of Neurophysiology at the Nobel Institute, Karolinska Institute, Stockholm;* Marcel GUILLOT, *Professor in the Faculty of Pharmacy, Paris;* Jean HAMBURGER, *Professor of Clinical Medicine and consultant to the Hôpital Necker, Paris;* Corneille HEYMANS, *Professor of Pharmacology at the University of Ghent, Belgium;* Herbert H. JASPER, *Ph.D., M.D., Professor at the Neurological Institute, McGill University, Montreal;* Pierre JEAN, *M.D., Institute of Medicine and Experimental Surgery, Montreal;* Bernard KATZ, *F.R.S., Professor of Biophysics, University College, London;* Yves LE GRAND, *Professor at the National Museum of Natural History and the Institute of Optics, Paris;* Jean MALMÉJAC, *Professor of Physiology in the Faculty of Medicine, Algiers, and Corresponding Member of the Academy of Medicine, Paris;* Hubert MAMO, *D-ès-Sc., formerly Head of the Clinical Department, La Saltpêtrière, Paris;* Rodolfo MARGARIA, *Member of the Academia dei Lincei, Professor of Physiology at the University of Milan;* Paul MOUREAU, *Professor in the Faculty of Medicine, Liège, Member of the Royal Belgian Academy of Medicine;* William RUSHTON, *F.R.S., Professor of Physiology at the University of Cambridge;* Jean-Pierre SOULIER, *Professor and Director of the National Centre of Blood Transfusion, Paris;* Robert STÄMPFLI, *Professor of Physiology at the University of the Saar, Homberg, Germany;* Joseph STOLKOWSKI, *Professor in the Faculty of Sciences, Paris;* Pierre VENDRYÈS, *M.D., Paris;* Yngve ZOTTERMAN, *Director of the Department of Physiology, Veterinary College, Stockholm, Sweden.*

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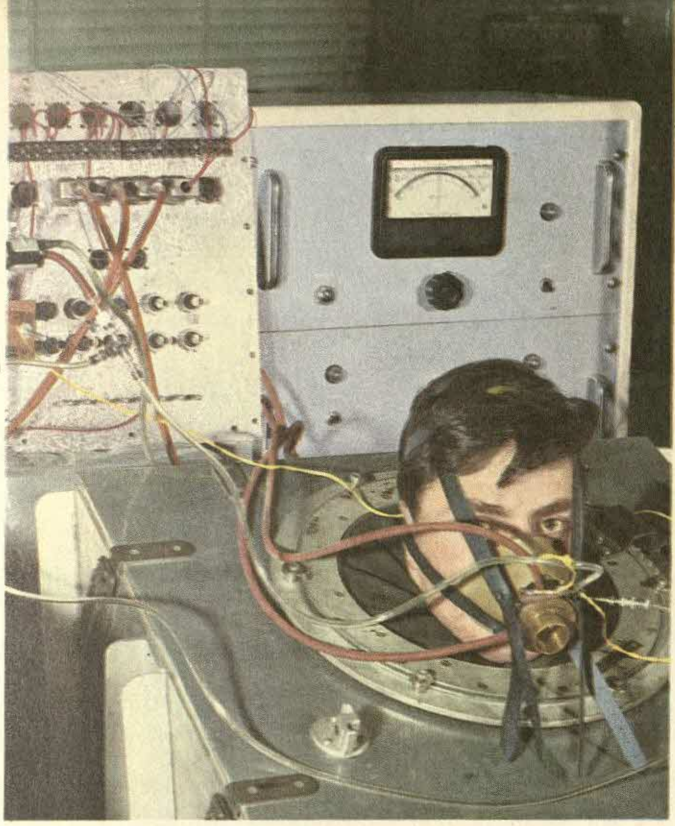
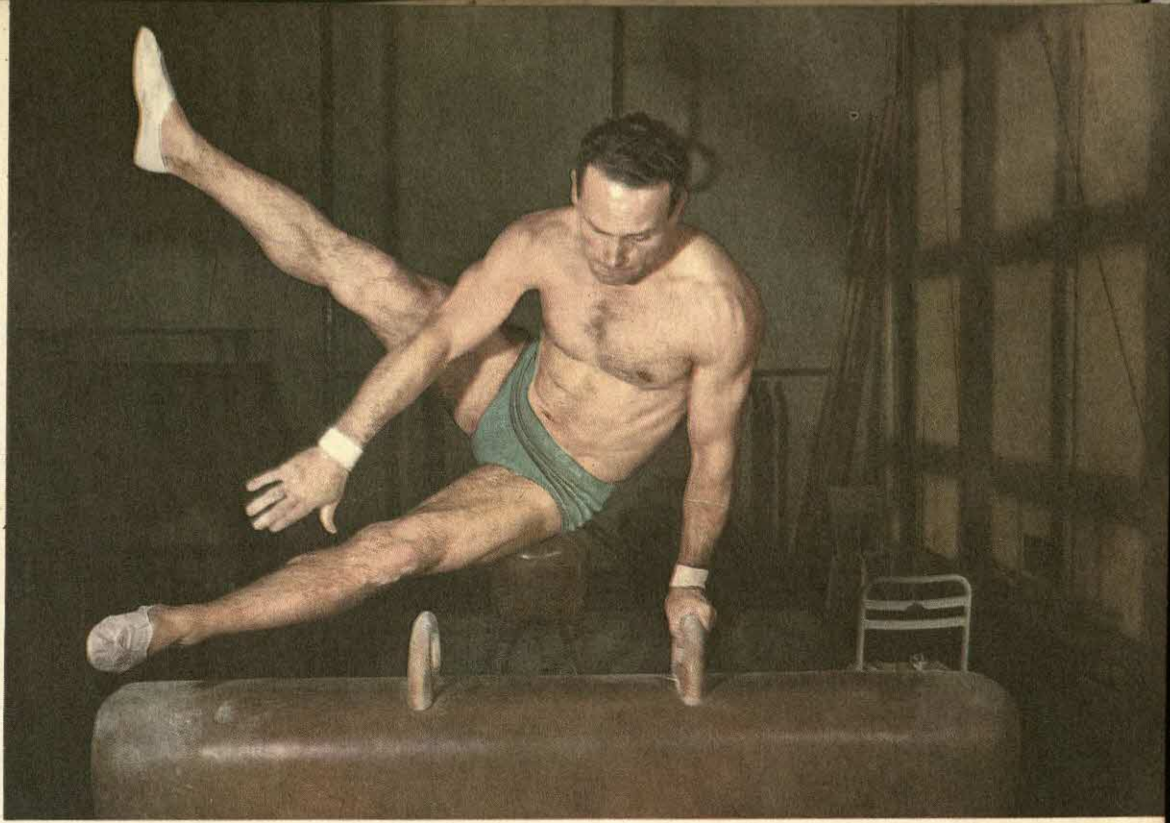
*EVERY book has an aim. That of the authors of the present work is very simple: to give the reader a knowledge of the human organism and enable him to admire its wonderful machinery.*

*All living organisms, even the simplest, are endowed with marvels: these are the mechanisms which allow them to live and reproduce in severe conditions which sometimes seem as though they would destroy all life. Certain algae manage to live in the scalding hot water of the Oregon geysers, and although all living organisms are well-adapted to certain surroundings, man alone can survive under a wide variety of conditions. His adaptability as an organism surpasses that of all others. What animal could accomplish such diverse and arduous actions as the ascent of the peaks of the Himalayas in rarefied air, or swimming the Channel? The human body is thus capable of exploits that only specialized mammals, such as the chamois and the dolphin, can achieve. In a way, man even develops the use of his organs and improves their efficiency. This may be illustrated by some of the popular sports, such as swimming rapidly by skilful strokes or making lightning descents on skis. What is man's secret in overcoming the weaknesses of his body? This is easily named, though difficult to define: it is his will. In other words, it is the ever-present idea of a physical or moral goal to be reached, an idea which belongs to man alone. There are two conditions for its pursuit: consciousness and memory, which, we can say without vanity, are integrated to the highest degree in the human mind.*

*Another characteristic aspect of man's highly developed state is the creation of artificial organs. In this way appeared the prehistoric chipped flint implements and the infinitely varied and specialized machines and instruments necessary to the many aspects of modern technology. It is not absurd to consider the creation of machines by man as a real process of evolution, similar to that which, through the geological ages, has endowed all animals and plants with more and more highly developed organs. Man alone, however, has been capable of profiting from this and has extended his mastery over the external world. It is from this experience that his capacity to control himself is undoubtedly derived.*





*Among other organs evolved by man are his visual and auditory organs whose exquisite sensitivity approaches the maximum that is theoretically possible. The cells of the retina of many animals, like those of man, react to one or two units or* quanta *of light. It is not possible to improve this near perfection, but man has managed to extend its effectiveness. Just as the tool 'lengthens' the hand, the telescope, the microscope and the television camera lengthen sight. Machines show that evolution continues beyond the physical limits of the human body. Some particularly successful machines created by man even take on the aspect of living creatures when they are well-designed. Such were the beautiful sailing ships of old, and such are intercontinental airliners of today. Both keep on their course, correcting the lurches caused by waves or air-pockets, with no intervention from the pilot. Here again evolution seems to have proceeded as everywhere else, by trial and error, although by a shorter path. In both cases ill-equipped machines have not survived; frail ships have been destroyed by storms, unsafe planes have crashed to the ground.*

*Is this wonderful machine, the human body, the exclusive product of evolution, or does it result also from divine intervention? These are ever-recurring problems, because they are peculiar to man. He finds it difficult to apprehend the divinity, but willingly believes that he is made in God's image; for the Greek sculptors have taught him that his body enshrines the supreme harmony. The 'human machine', although a divine image and the embodiment of beauty, itself the vehicle of the intelligence and conscience, nevertheless resembles in many of its features any other mammal, such as the dog or the monkey, which Descartes considered as 'machines'. But man possesses a far more important nervous system, composed of parts which are not themselves superior in essence but which are much more numerous. Nevertheless, the number of nerve cells cannot in itself account for man's faculties. The multiplicity of relations between these cells, that is to say, their assemblage, is all-important, and as a result 'the whole is more than the sum of its parts'. This assertion applies to varied fields. A particularly obvious example is the human brain, which takes part in the immaterial universe of ideas and feelings, a universe which is very real but impossible to measure quantitatively. How can man's brain and organs, that is, his own 'machine', be at once the shelter and the means of expression of the mind? There is no objective, final and complete solution to this problem, but it is possible that it may soon be partially solved.*

*This is the reason for the place given in this book to the nervous functions. The central chapter is indeed entitled 'The Neurophysiological Basis of the Mind'; yet the nervous functions cannot develop without the participation of all the others, even the simplest. For instance, the neurones of our cerebral cortex respire actively,*

*imperiously calling for oxygen, which is brought to them by the circulating blood. If this is interrupted, even for a few moments, they are injured beyond repair.*

*All the organs of the body are thus linked by many precise connections. None can survive for long without the aid of almost all the others. The interdependence of these mechanisms makes the study of the human machine extremely complicated. It seems even to exclude the very principle of such a study, since, to be rigorous, the analysis of one organic function requires the simultaneous analysis of all the others, which is beyond our faculties of intelligence. The different functions are therefore studied one after another, according to an arbitrary order arrived at by a long academic tradition. The student who begins to read an elementary textbook of physiology for the first time is somewhat confused: it is only at the end of the book that the difficulties of the beginning are resolved. The working of the first organs studied becomes clearer as the various influences of the different functions on each other become apparent. A second reading of the book is necessary. In any case, the reader's knowledge will be strictly limited, in spite of his efforts; for the human body, even those parts of it which are actually known, is a vast field of study. A lifetime is not enough for the physiologist to survey and acquire a personal knowledge of the whole human body; the same applies to the geographer and his study of the earth. Nearly three thousand million individuals people the earth. The occupation and life of each influences the activity and life of all of them, yet who would think of attempting to understand the part played at every moment by each man or even by each of the main groups? How many actions, how many thoughts, though of momentous importance, remain unknown even within the smallest communities?*

*In the same way, every human organ contains innumerable entities, distinct although interdependent: these are the cells. The cerebral cortex itself contains nearly ten thousand million of them. On the other hand, each of our cells is itself a universe, a molecular universe. A cell of average size, weighing a few millionths of a milligram, may, for example, contain ten thousand million molecules, taking into account only the biggest, the protein molecules, of infinitely varied structure and chemical reactivity. Who, then, could hope to learn the form, function and biochemical architecture of all the cells and of their extremely diverse aggregate?*

*Without presumption, more limited aims are, however, accessible. Anyone wishing to inquire into the life of our planet will find enjoyment and benefit in merely studying certain aspects of it, for instance, the constitutions by which the nations are governed, and the institutions and means of transport which determine the relations between them.*

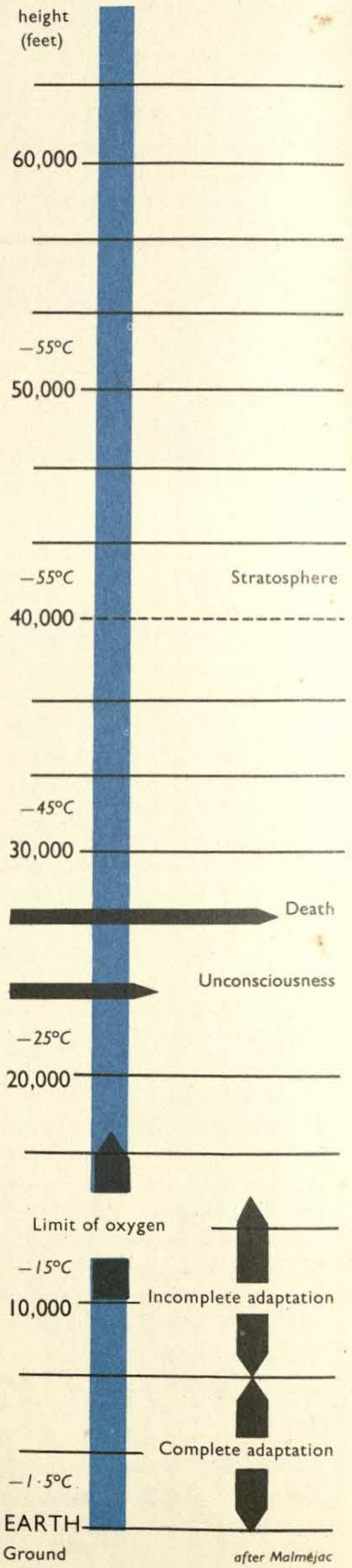
*Such a study with limited objectives may, nevertheless, lead to interesting discoveries. The physiologist will also limit himself to the study of some particular types of function. This deliberate limitation of the field of study does not imply a narrow outlook. It is the condition of the exactitude and of the rigour of the study wherein lies the hope of discovery.*

*Knowledge of physiology contains a kind of indeterminacy principle. I have previously supported this affirmation with a comparison actually drawn from man-made machines. No one is capable of describing accurately all the mechanisms which go to make up a machine so highly developed as the modern aeroplane. An exact description of its parts requires the co-operation of many people, specializing in different aspects, from engines to telecommunications. The more general knowledge becomes, the further it strays from the details which define reality, until finally it merges in a common but meaningless definition, comprising things so disparate as an aeroplane and a living organism, on the basis that both derive energy for their movement from the oxidation of certain substances.*

*The present work is a modest expression of the above principles. It gives but a few glimpses of human physiology. The reasons for the authors describing one particular aspect rather than another are very simple: since both by its nature and scope the subject defies any general description, those points were selected which appeared most likely to maintain the interest of the contemporary reader.*

*Alexandre MONNIER*

LIMITS OF RESISTANCE
OF THE HUMAN MACHINE



*after Malméjac*

## PART ONE

# *The main services*

Single-celled living organisms possess all the apparatus necessary for existence and reproduction, assembled in some hundreds or thousands of cubic microns of protoplasm. This extremely concentrated apparatus is in the form of batteries of enzymes and molecular structures.

Higher in the animal scale among simple multicellular animals (primitive invertebrates, such as the coelenterates) the increased volume and complexity of the organism call for specialization by the different cells, which tend to gather into tissues for the fulfilment of a distinct physiological function. Within the same zoological groups another example of this same tendency can be seen: the individuals gather into a single colony in which each displays an almost homogeneous cellular structure, since each specializes in one definite function, such as nutrition or reproduction.

In the case of the more complex metazoa, the division of labour within a single organism is carried much further. Not only do the cells change and specialize with a view to this or that function, but cells of similar structure associate to form tissues, which are grouped into organs of complex morphology, themselves grouped within systems each devoted to a particular function, or main service. These very diverse functions may, however, be divided into a few important categories: first, the so-called nutritional functions, which provide the cells with the substances necessary for their functioning and survival: second, digestion, respiration and circulation; third, the functions of excretion, required to eliminate the waste products of the metabolism of cells, and reproduction, whose role is the perpetuation of the species. The entire set of secretions of the endocrine glands maintains the balance, regulates the growth, and co-ordinates the functioning of the organs. It is powerfully backed up by the autonomic nervous system (sympathetic and parasympathetic systems) to ensure the harmonious and smooth working of the whole.

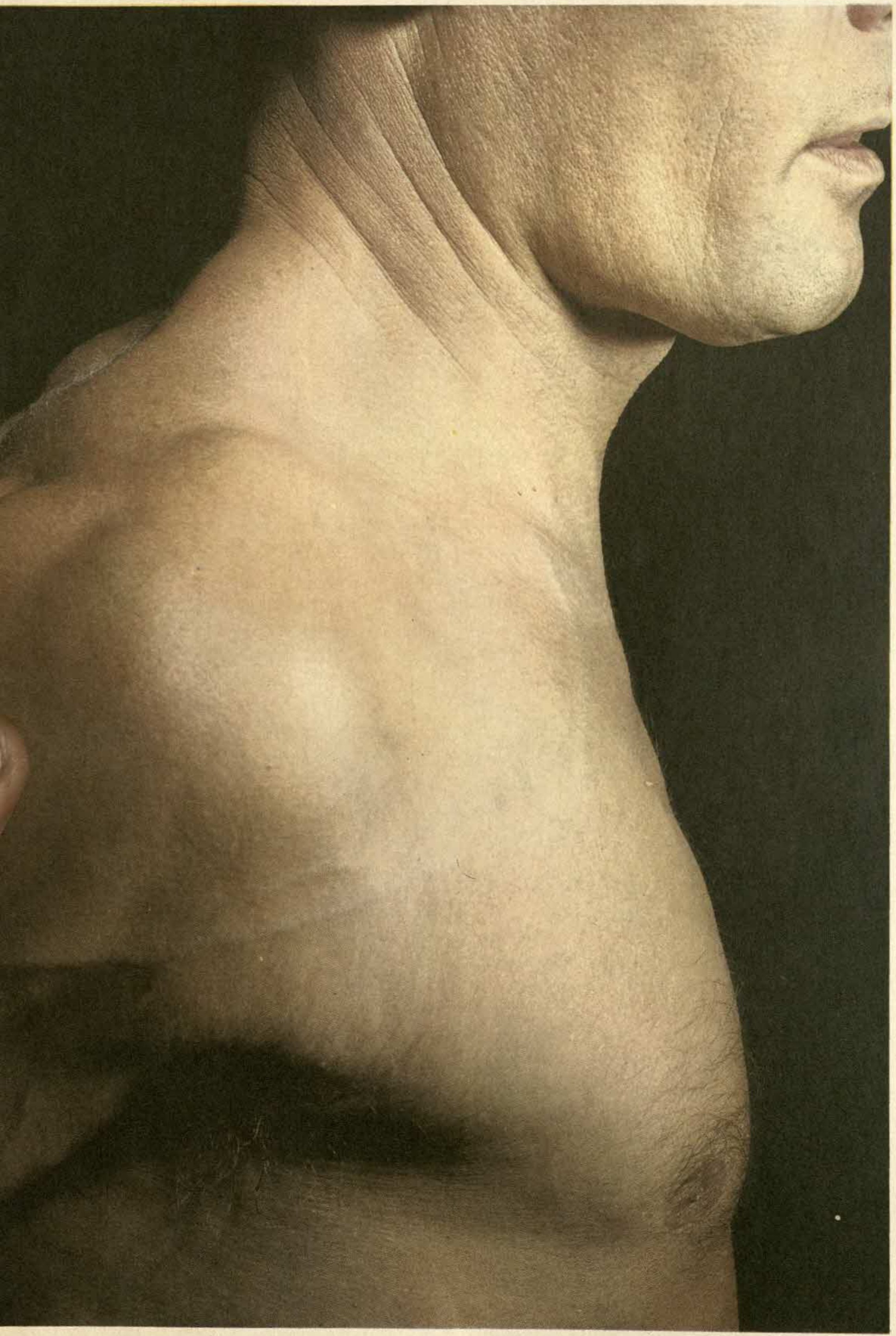
An animal organism could not survive if it were not capable of adapting itself to all the fluctuations in the surroundings in which it lives. This implies that the organism must obtain information about its environment and be able to face it. This is the part played by the functions of communication, which, through the sense organs, keep the organism informed of all the favourable or unfavourable alterations in the surrounding world, and, through the nervous system, co-ordinate all its resources so that it can react and adapt itself to these changes. By the ordered contraction of the muscles, the set of functions of motility ensures the movement of the articulated bones of the skeleton, thus enabling the organism to approach or to flee, and giving it a remarkable autonomy with respect to the outside world.

The functions of communication, in association with particularly sensitive and complex regulatory mechanisms, unquestionably find their culmination in the human species. It is for this reason that they have been given a particularly important place in this work. Other functions must not be forgotten, however, and *primum vivere* is the most evident truism for physiologists.

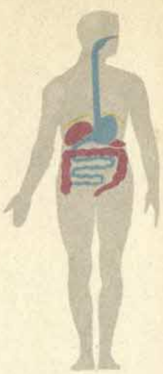
The pages which follow describe the remarkable machinery for ensuring the continuation and functioning of the main services by which the thousands of millions of cells that form our organism find the conditions of their existence fulfilled.

General diagrams giving an idea of the chief functions—respiration, circulation, and digestion—are followed by two characteristic examples of the main services: the respiratory system and the kidney function. The extraordinary complexity of the human machine compels us to make a choice and instead of describing the mechanism of organs (heart, stomach, liver) which are already treated exhaustively in every textbook of physiology, we have preferred, as an introduction, to look into the subtle 'regulations' of life: respiration and elimination.

# *Four main services*



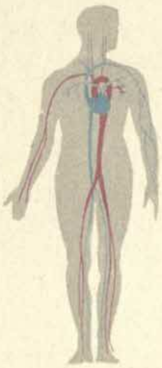
*The histological preparations were provided by the laboratories of Pathological Anatomy of the Hôpital Saint-Antoine, Paris: Professor Jean Gosset (preparations by Madeleine Boucher), Professor Raoul Kourilsky (preparations by Mme Russon), and Professor Boudin.*



## The digestive system

*The digestive system transforms the nutrients that are absorbed by man, which are often composed of very complex chemical compounds, into simpler substances which can be directly assimilated by the cells. The mechanically triturated nutrient substances are subjected all along the digestive tract to the powerful action of the digestive juices which break them down into simpler molecules, by innumerable hydrolytic processes. Thus, sugars are transformed into glucose, lipids into fatty acids, proteins into amino acids. When all that can be utilized by the organism has passed into the blood, the remaining excrementitious products are eliminated.*

*(a) the liver*
*(b) a fragment of hepatic tissue*
*(c) a fragment of pancreatic tissue*
*(d) lining of the stomach*



## The circulatory system

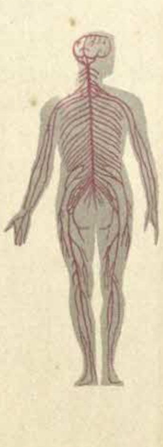
*The role of the circulatory system is continuously to ensure to the organism's billions of cells the supply of nutrient substances and the oxygen necessary for their survival. At the same time, it eliminates the waste products of their metabolism. It is also responsible for the transport of certain complex and valuable substances: these are the hormones, which ensure the growth and harmonious functioning of the different organs. The blood, which is constantly renewed and circulates through the vascular system under the powerful pumping action of the heart, carries out these delicate functions, and also ensures the defence of the whole organism against the attacks of germs or viruses.*

*(a) the veins of the cerebellum*
*(b) tissue of a cardiac artery*
*(c) segment of an artery*
*(d) mitosis in a blood cell*

## The respiratory system

*The respiratory system ensures that the tissues' need of oxygen is met, and that there is evacuation of carbon dioxide, the final stage in cellular oxidation. The air breathed in inflates and fills the lungs, which are enlarged through the action of the respiratory muscles. The oxygen crosses the thin wall of the pulmonary alveoli and combines with the haemoglobin in the red corpuscles. At the same time, these corpuscles release the carbon dioxide that they have taken up within the tissues. The carbon dioxide crosses the alveolar walls in the opposite direction to the oxygen and is eliminated by expiration, in the course of which the volume of the lungs is reduced under the effect of the decrease in volume of the thoracic cavity.*

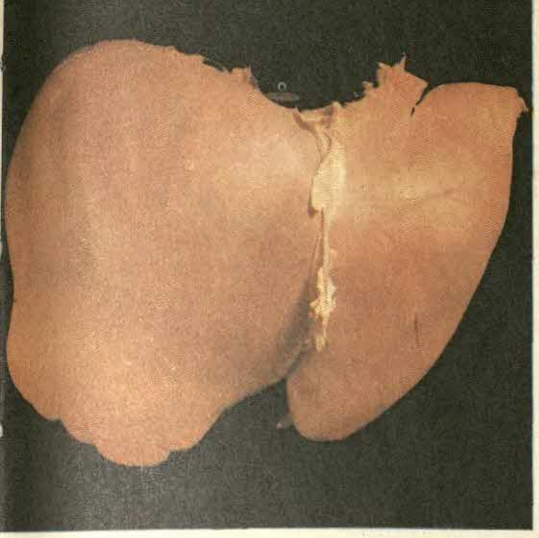
*(a) a lung*
*(b) a cartilaginous bronchus*
*(c) a bronchiole*
*(d) a pulmonary alveolus*



## The nervous system

*The nervous system is responsible for the links with the external world through the intermediary of the sense organs. The impulses despatched at high speed through the sensory nerves are sorted in the relay centres and from here they are directed to the cerebral cortex where they produce conscious sensations. From the nerve centres (brain, cerebellum, brain stem, spinal cord, ganglia of the sympathetic nervous system) an uninterrupted outward flow of nervous impulses will prompt, regulate and co-ordinate all the reactions of the organism to changes in its surroundings, while controlling movement, ensuring the satisfaction of the needs of the organism, and carrying out the orders of the mind.*

*(a) the brain*
*(b) the taste buds*
*(c) club cells of the cerebellum*
*(d) pyramidal cells*



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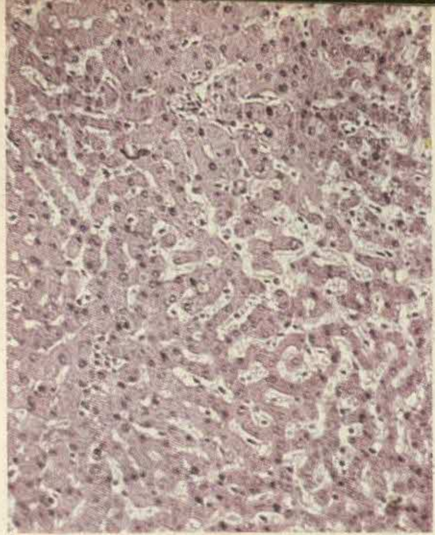

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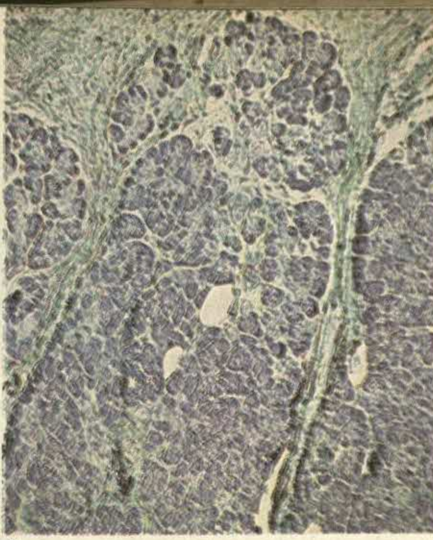

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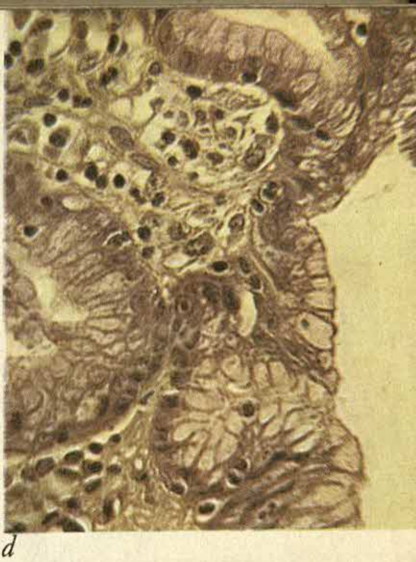

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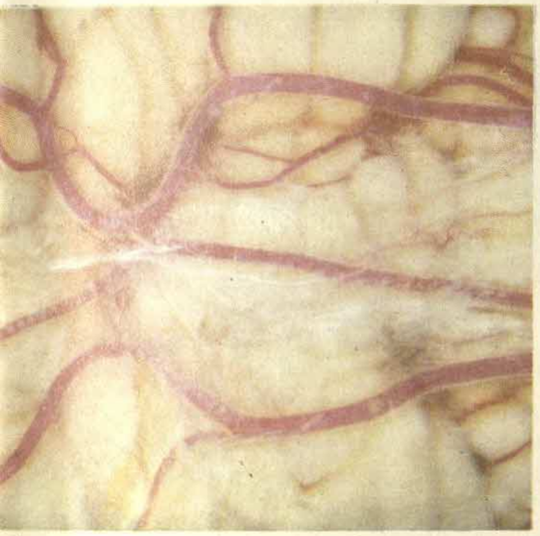

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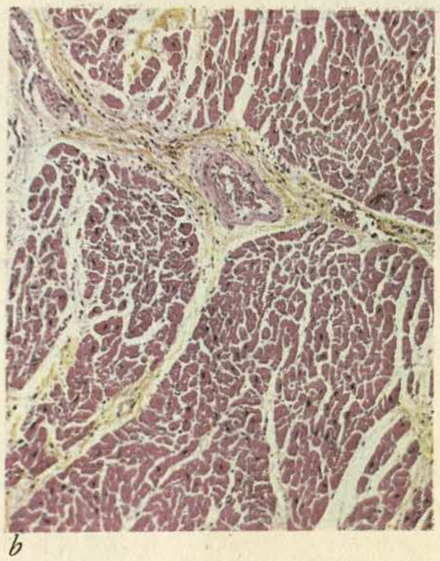

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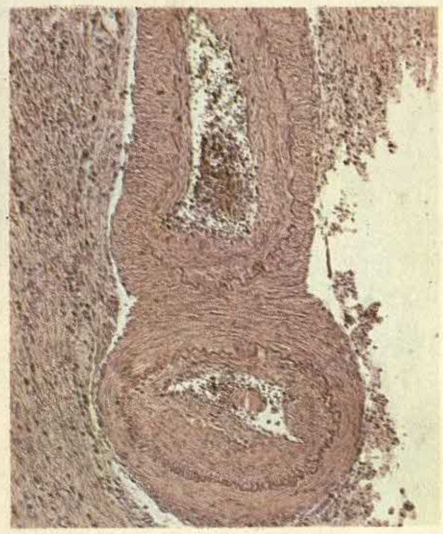

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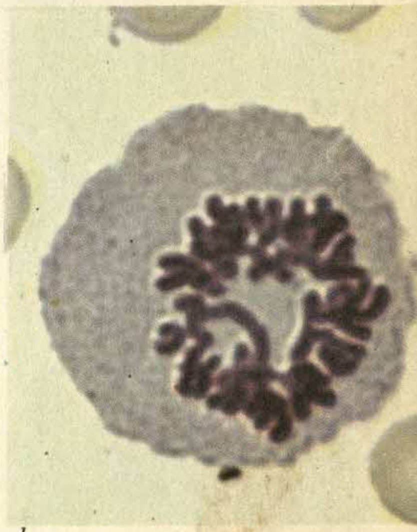

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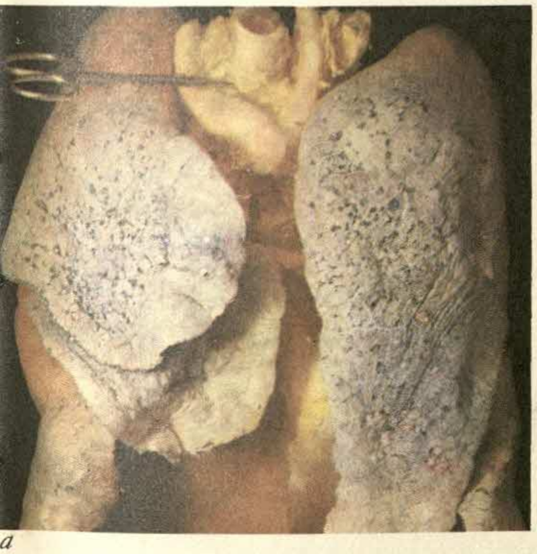

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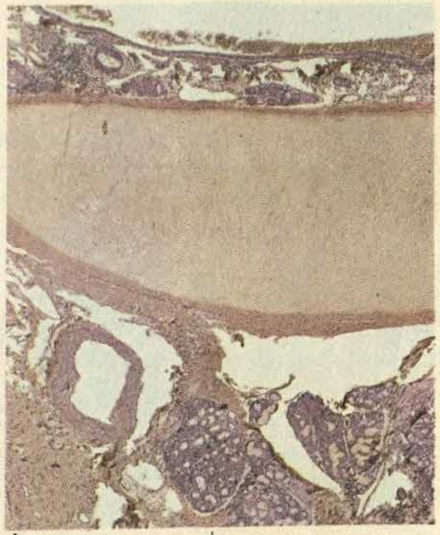

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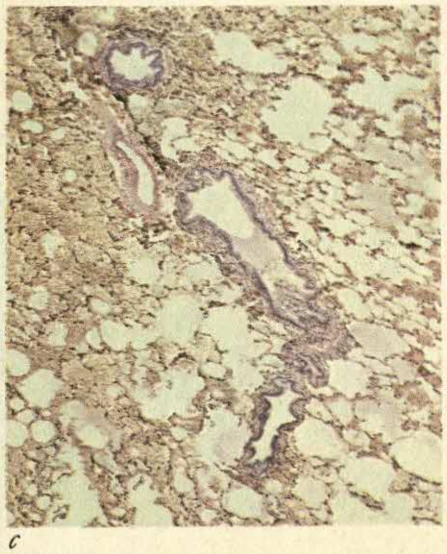

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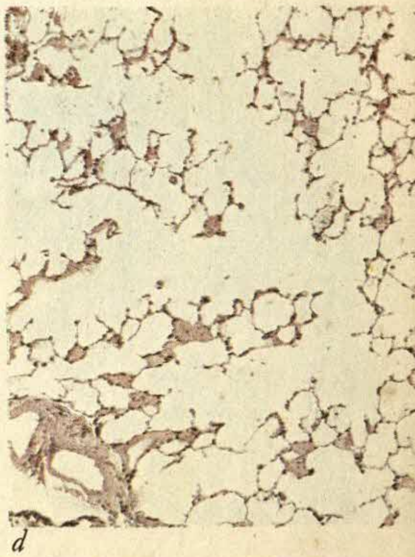

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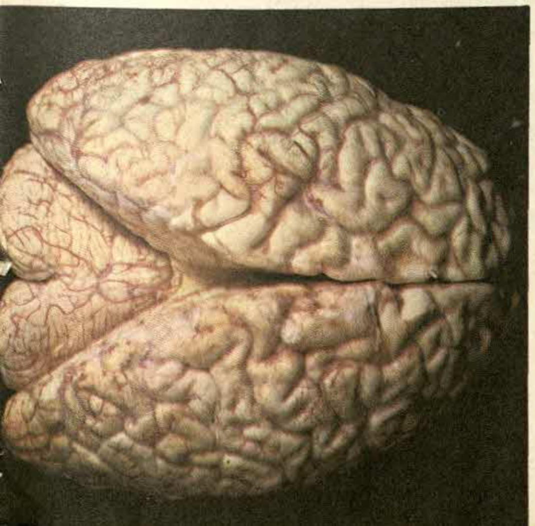
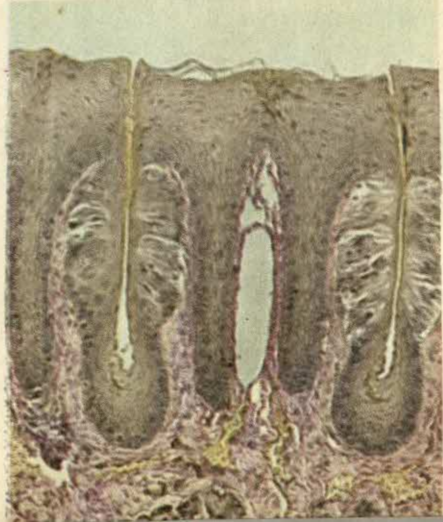
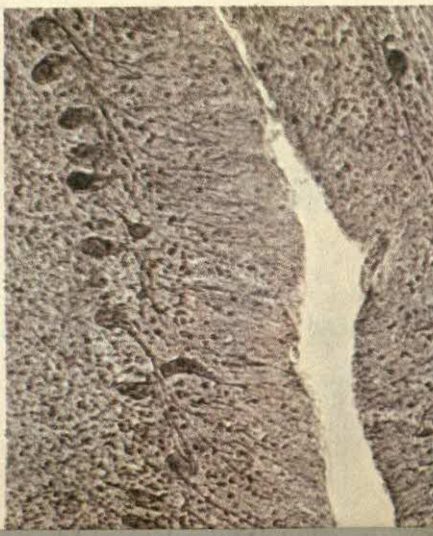
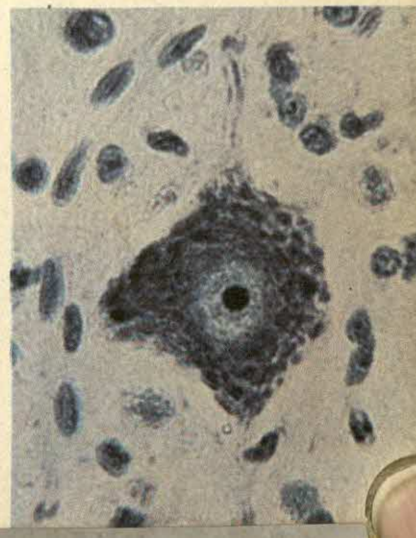








# Respiration

*Rodolfo MARGARIA*

*The transformation of energy, which takes place in all living organisms and is their distinguishing feature, provides the mechanical, electrical and especially the chemical energy required for the elaboration of tissues and other specific substances (secretions and excretions). In the last resort, all this energy results from the energy of combustion of the several substances brought in from the outside, namely, food. The combustion process is no other than that of oxidation: oxygen is drawn from the atmosphere and it is to the atmosphere that some of the products resulting from combustion, such as carbon dioxide, and to a certain extent water vapour, are returned.*

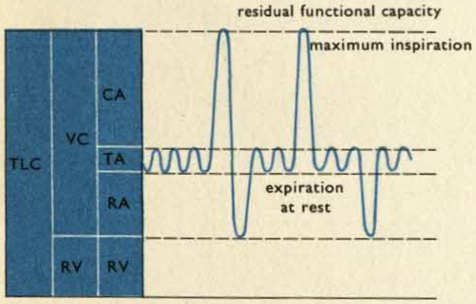


*Fig. 1. Variation in the capacity of the lungs during normal and forced respiratory movements of a person at rest. The volumes of pulmonary capacity indicated on the left are:* TLC *(total lung capacity),* VC *(vital capacity),* RV *(residual volume),* CA *and* RA *(complemental air and reserve air respectively),* TA *(tidal air).*

The term 'respiration' means the exchange of gases (oxygen and carbon dioxide) which takes place between the living organism and the environment.

In higher organisms this exchange takes place at several different levels. An initial exchange must occur between the air in the lungs, from which the oxygen is continually taken up and into which carbon dioxide is continually poured, and the external air. This is the process of external respiration.

The composition of the air inside the lungs—and more precisely in the interior of the alveoli, with the dense network of blood capillaries, involved in the exchange of gases with the alveolar air—is different from that of the inhaled air, since it depends both on the exchanges between the external air and the air in the lungs, and on the exchange of gases between the blood circulating in the lungs and the air in the alveoli. The composition of alveolar air is very constant, especially the content of carbon dioxide, the partial pressure of which is normally 40 mm of mercury. This constancy is the result of a subtle self-regulating mechanism by which the respiratory activity is governed by the amount of carbon dioxide which must be eliminated from the organism.

The pulmonary tissue is composed of a web supporting the blood capillaries which constitute the walls of the alveoli, and the tracts (bronchi and bronchioles) through which air is brought to the alveoli themselves.

The alveoli appear as small cavities, more or less spherical and varying from 0·1 to 0·3 mm in diameter, of which there are about 100 million. They possess an extremely slender wall, in the thickness of which are found the blood capillaries arising from the fine ramifications of the pulmonary artery. Here the venous blood from all parts of the organism takes up oxygen and releases carbon dioxide. Each capillary is about 1 mm long, and the total length of the capillaries is about 1,500 miles. Because their diameter is minute—similar to that of an erythrocyte (8 microns)—the total area of the pulmonary capillaries is of the order of 60 to 70 square yards. It is across this surface that the exchange of gases between the blood and the pulmonary alveoli takes place, facilitated by the thinness of the membrane, which is only 0·3 micron thick. This is known as the respiratory function of the blood. The blood which has been oxygenated by this exchange passes to the left side of the heart, then to the arterial system, and finally to all the tissues, through the fine tubes of the blood capillaries. The exchange of gases is caused by the physical process of diffusion of the oxygen from the blood. The partial pressure of the oxygen in the blood is higher than the pressure of this gas in the tissues, for it is continually being removed and used up in the processes of combustion. The exchange of carbon dioxide takes place in the opposite direction, because its partial pressure is higher in the tissues than in the blood.

The use of oxygen for combustion in the tissues, and the formation of carbon dioxide, is known as cellular respiration.

The exchange of gases varies according to the size and activity of the organism. In man at rest the absorption of oxygen reaches about 0·25 litre a minute and the elimination of carbon dioxide 0·2 litre. At a time of maximum muscular activity, the consumption of oxygen and the production of carbon dioxide may both exceed 4 litres a minute.

## *The mechanism of respiration*

The movement of air into the lungs is brought about by an increase in the volume of the thoracic cavity with the action of the respiratory muscles. The lungs, which adhere to the interior wall of the cavity—by means of an extremely thin film of pleural fluid—follow this movement passively. Some of the inspiratory muscles have a fixed point on the ribs; by raising the ribs, the muscles increase the antero-posterior and transverse diameters of the thoracic cavity (costal respiration). Another important muscle is the diaphragm, a thin dome-shaped 'sheet', which closes the lower part of the thorax and separates it from the abdomen. The diaphragm contracts and flattens, contributing in this way to the extension of the vertical diameter of the thoracic cavity and raising the ribs (abdominal respiration). At the time of expiration, the thorax returns to its initial position, either through the elasticity of the thoracic wall, or through the activity of the expiratory muscles: air is expelled through the same tracts that were used by fresh air during inspiration.

This in-and-out respiratory movement is not a perfect system, for no exchange takes place within the respiratory tracts (trachea, bronchi and their ramifications). In the respiratory system of insects air goes in from one side, spreads throughout the 'trachea' which lead to the tissues, and is expelled through different tracts. In mammals, on the other hand, all the air breathed in does not reach the lungs. The volume of the respiratory tracts is about 150 cc. In a single respiration at rest the thoracic capacity increases by 500 cc, so that only 350 cc of air succeeds in reaching the alveolar cavities: the 150 cc left in the respiratory passages is expelled in the next respiration without being used. This volume is known as the respiratory dead space.

The volume of air which is taken into the thorax during each inspiration is known as *tidal air*. Following a normal inspiration, it is possible to introduce an additional quantity of air into the thorax by a violent inspiration. This extra volume of air inhaled is called *complemental air*. Similarly, after a quiet expiration, it is possible by a violent expiration to blow out of the thorax a further volume of air called *reserve* or *supplemental air*. The sum of the tidal air, complemental air and reserve air is given the rather unsatisfactory name of *vital capacity*. This varies with the size of the individual, and to a certain extent with the anatomy and functioning of the respiratory system. The normal vital capacity of a man is from 4 to 5 litres (fig. 1).

It is not possible, however, even after a forced expiration, to expel all the air from the lungs; a certain quantity remains, about 1·2 litres, which is called *residual air*, and this increases considerably in 'pulmonary emphysema', a pathological condition frequent in old age.

In an individual at rest the number of inspirations per minute is 10 to 15: the *pulmonary ventilation*, or the volume of air passing through the respiratory system each minute, is expressed by the product of the frequency and the volume of respiration, and is of the order of 6 litres per minute: during intense muscular activity the rate of inspiration may rise to 50 and the ventilation to 150 litres or more per minute.

The main functional features of the respiratory system are mechanical. They are determined by the extensory power and elasticity of the thoracic wall of the lungs, and by the resistance encountered by the air within the respiratory tracts as it is breathed in and out of the lungs.

The mechanical characteristics of the thoracic cavity and lungs together can be studied quantitatively and with accuracy, by establishing a pressure-volume diagram. This is made by measuring the pressure reached in the lungs when a given volume of air is introduced or removed, and when the data are plotted they result in a diagram and graphs such as those shown in fig. 2.

Very little work is normally involved in respiration, even during a violent muscular effort, since the volume of tidal air never reaches the vital capacity and the inspiratory and expiratory muscles are never completely contracted. It is possible, however, to measure the maximum respiratory work extremely accurately and this is an excellent way of

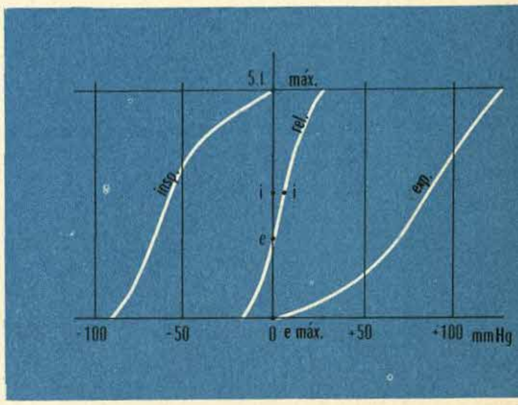
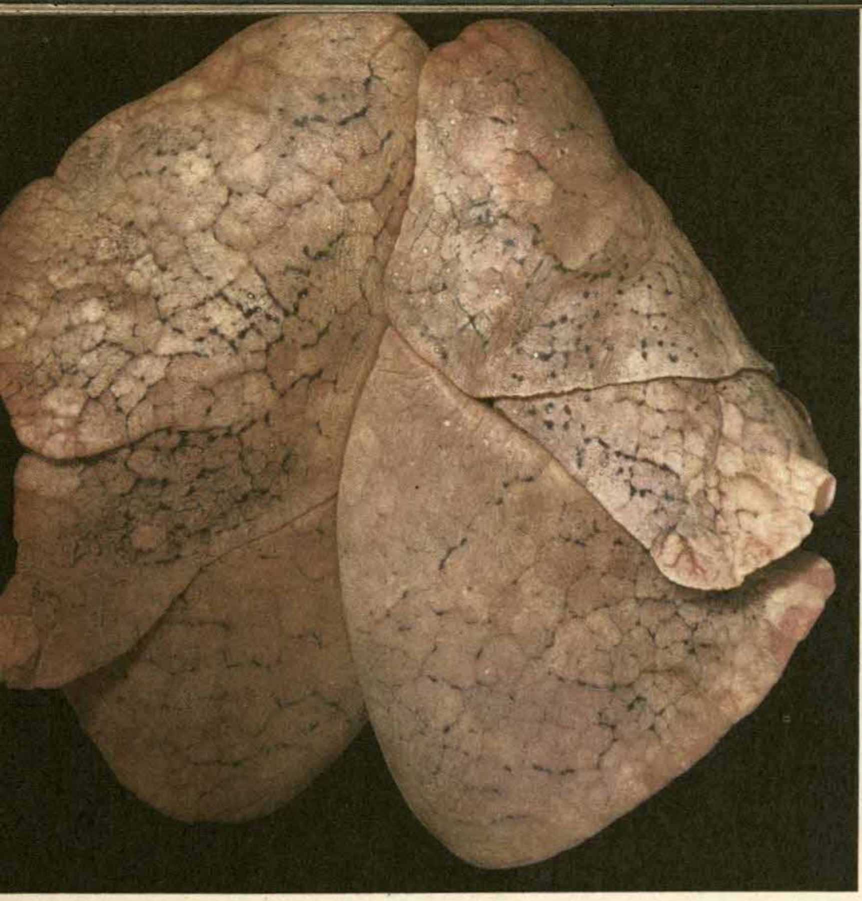
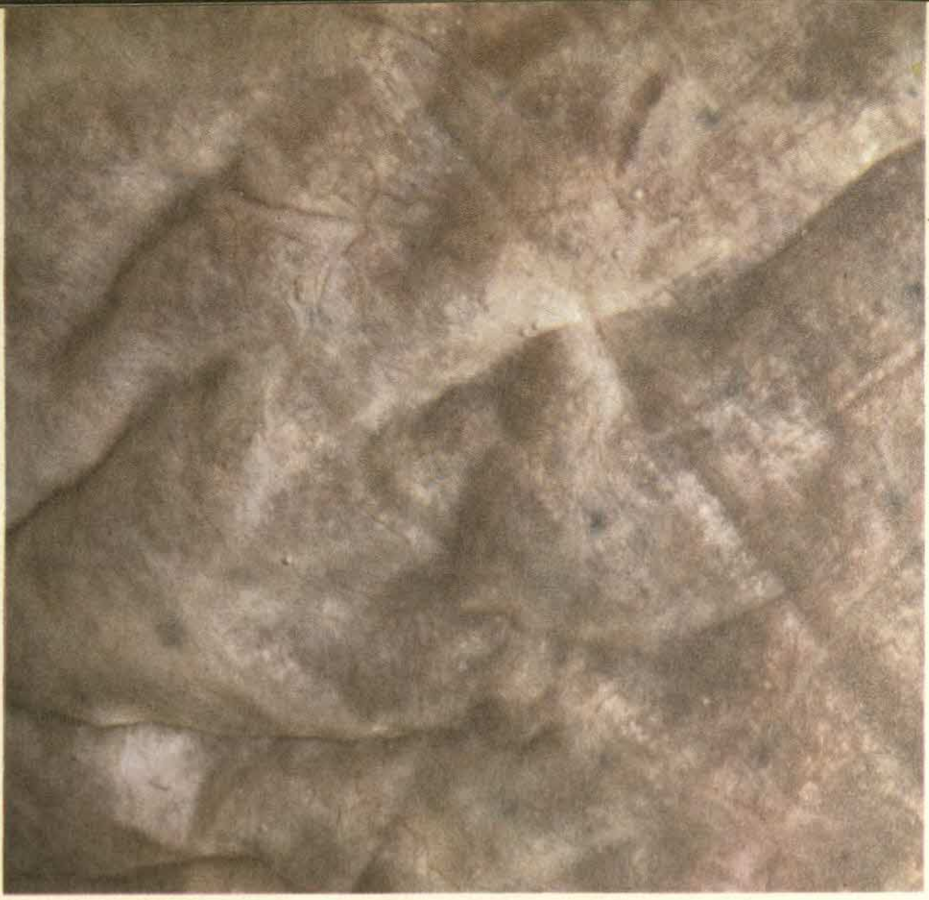


*Fig. 2. Pressure-volume graphs of the respiratory system. Ordinates: volumes in litres; abscissae: pressure in mm Hg. The curve* rel. *refers to the mechanical properties of the thorax (respiratory muscles relaxed). The curves* insp. *and* exp. *refer to the mechanical properties of the thorax (inspiratory and expiratory muscles at maximum contraction). The scale of volumes starts from the position of maximum expiration. The segment* $e_{max}$ $i_{max}$ *indicates the vital capacity, and* e, i, *the normal resting positions of expiration and inspiration.*

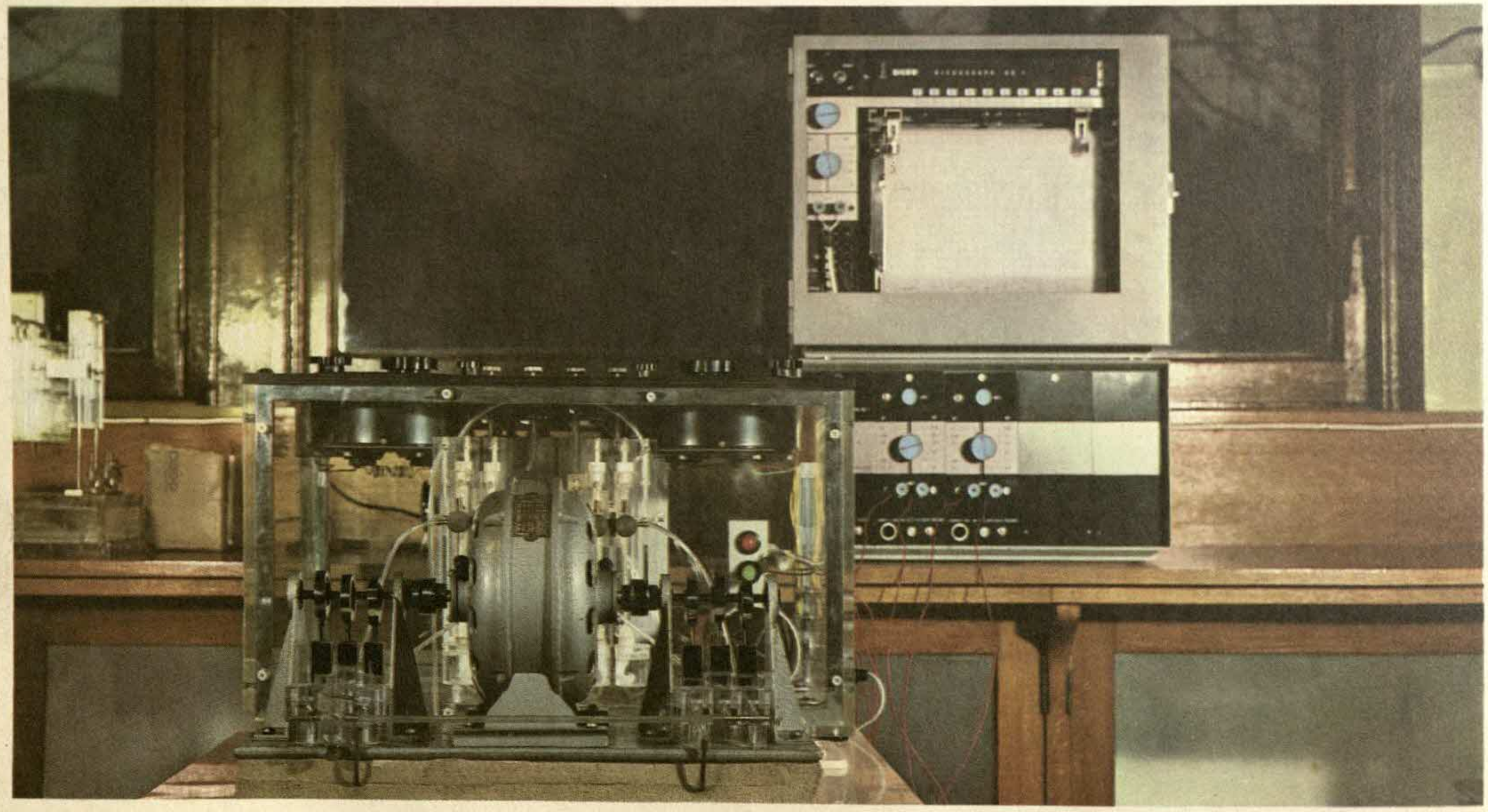


*The lungs seen from behind. The right lung is made up of three distinct lobes, the left lung of two. The dark spots are due to dust inhaled by a person who has lived all his life in a large town. (Photo Lod).*

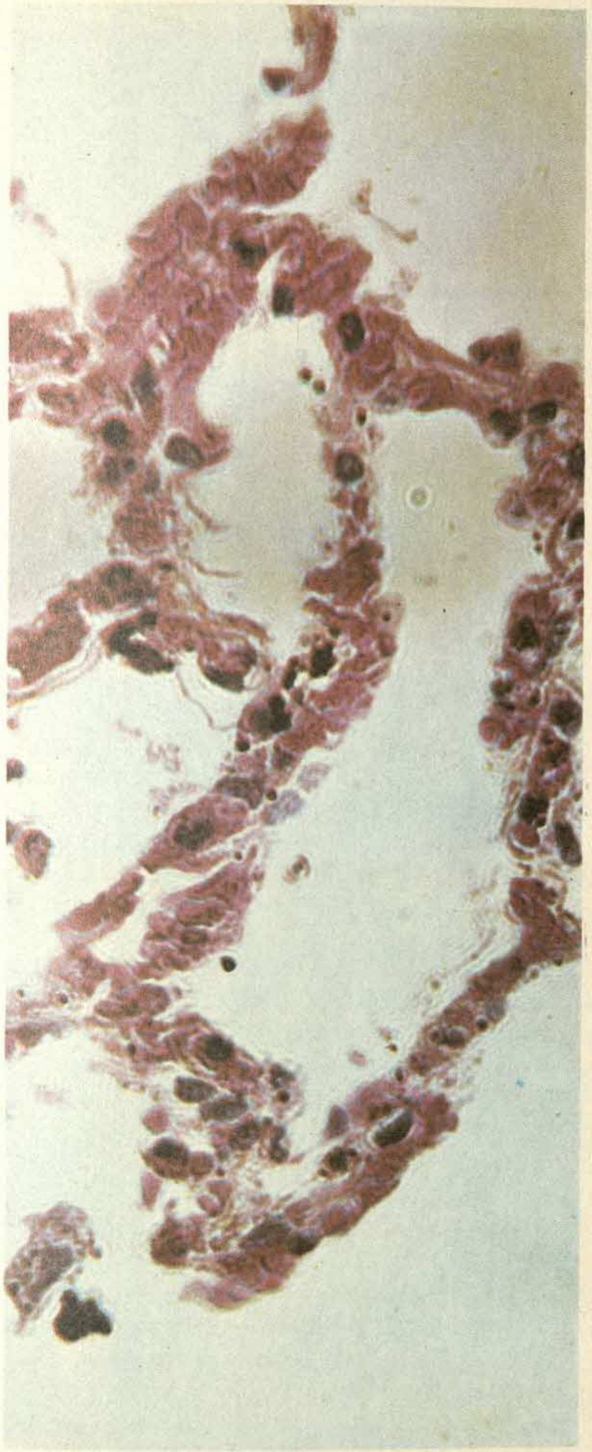


*The surface of a healthy lung; there are no dark spots of dust. (Photo Lod, taken in the laboratory of Professor Jean Gosset, Hôpital Saint-Antoine, Paris).*

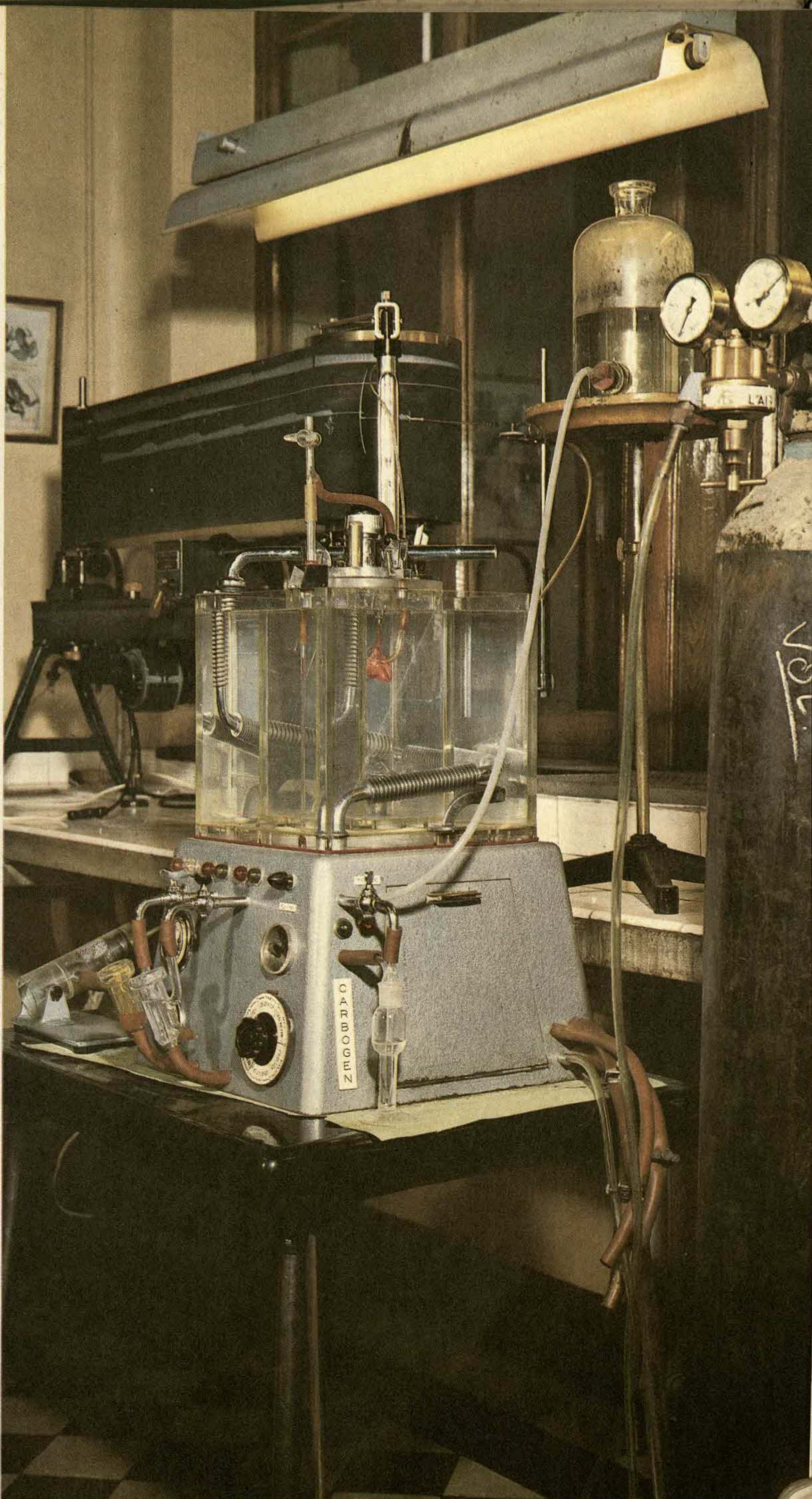
*Diaferometer with continuous recording of the oxygen and carbon dioxide contents of expired air. This apparatus enables determinations of metabolism to be made in man and animals by means of measurements of gaseous exchange. (Photo Lod, taken in the laboratory of Professor Heymans, Ghent).*



# *The lung*



*Section through an alveolus of a healthy lung. (Photo Lod, taken in the laboratory of Professor Jean Gosset, Hôpital Saint-Antoine, Paris).*



*Apparatus for the artificial perfusion and ventilation of isolated lungs. A recording of the reactions of the respiratory tract to pharmacological reagents administered through the circulation or inhaled as aerosols.*

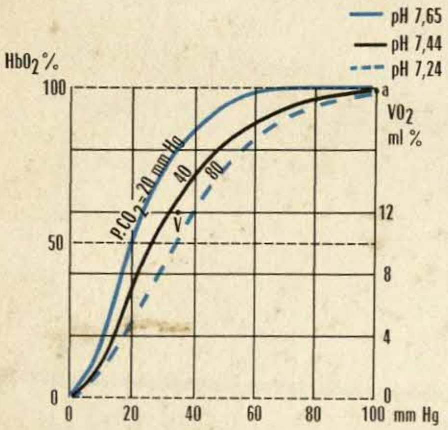


*Fig. 3. Oxygen dissociation curves of the haemoglobin of the blood. Ordinates: on the left, percentage saturation of haemoglobin with oxygen; on the right, cc of oxygen per 100 cc of blood combined with haemoglobin. Abscissae: partial pressure of oxygen ($PO_2$) in mm Hg. The three curves refer to the same blood in equilibrium with carbon dioxide at partial pressures of 20, 40, and 80 mm Hg respectively; a: arterial blood; v: venous blood. Note the effect of carbon dioxide and the increased acidity as the dissociation curve moves to the right.*

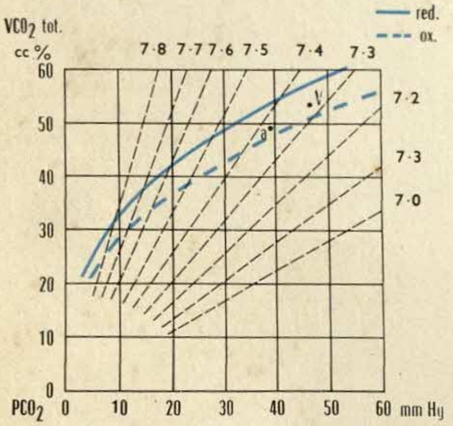


*Fig. 4. Carbon dioxide dissociation curve for oxygenated blood,* ox., *and reduced blood,* red. *Diagonal lines indicate pH at different points on the curve:* a, v, *points corresponding to arterial and venous blood; $VCO_2$ tot., total volume of $CO_2$ (cc %); $PCO_2$, partial pressure of $CO_2$ (mm Hg).*

verifying the functional condition of the respiratory system.

The work done by the respiratory muscles is expended to overcome not only the *elastic resistance* to extension of the thoracic wall, but also the *resistance to flow* of the air in the respiratory tracts. This resistance increases with the speed of the air in the respiratory tracts, and it can reach very high values during *muscular work*, or when the respiratory tracts are restricted by an accumulation of mucus or catarrh, or in a spasm of the muscles of the bronchioles, which is common in bronchial asthma.

The resistance R of the passages is expressed in terms of the pressure P necessary to obtain a given flow F; that is, by the difference in pressure between the environment and the pulmonary alveoli: R is expressed in millimetres of mercury or water necessary to maintain a flow of 1 litre per second: $R = P/F$.

The normal resistance is 1·5 mm Hg/l/sec. This means that when 1 litre of air is being expelled per second, the pressure in the alveoli is 1·5 mm Hg higher than the pressure in the mouth (barometric pressure). This is very easily measured in man by interrupting the flow at the level of the mouth for a moment (0·1 sec); the pressure in the whole respiratory system is equalized at once, and the pressure measured at the time of the interruption indicates the pressure in the lungs.

The elastic properties of the lung and of the thoracic wall may be studied separately from the respiratory system by measuring the pressure in the thoracic cavity, that is, in the space between the lung and the thoracic wall. This formerly necessitated a letting of blood or a pleural puncture, but it can now be done simply by introducing a small balloon connected to a quick-registering manometer into the lower third of the oesophagus.

## *The diffusion of gases in the lungs*

The exchange of gases which takes place between the alveolar air and the blood in the pulmonary capillary is a process of simple physical diffusion, without the intervention of any phenomena pertaining to life. This exchange is facilitated by the large surface of the capillaries and by the extreme thinness of the membrane which separates blood from air in the alveoli. It also depends, obviously, on the difference in partial pressure between the blood gases and those of the alveoli.

The capacity for diffusion is, in the case of oxygen, given by the number of cc of oxygen traversing the membrane per minute for each millimetre of mercury (mm Hg) pressure gradient. This is normally 25 at rest, which means that 250 cc of oxygen per minute will be absorbed into the blood from the lungs, if the partial pressure of the oxygen in the alveoli is 10 mm Hg higher than in the pulmonary capillaries. During muscular effort the capacity for diffusion increases to about 80 and there is a corresponding increase in the irrigation of the lungs by the blood.

This capacity decreases appreciably in pulmonary emphysema, owing to the deficiency of a great number of the capillaries, and in oedema of the lung because of the thickening of the membrane. In such cases the patient's respiration is helped if oxygen is administered, thus increasing the oxygen pressure gradient between alveoli and capillaries.

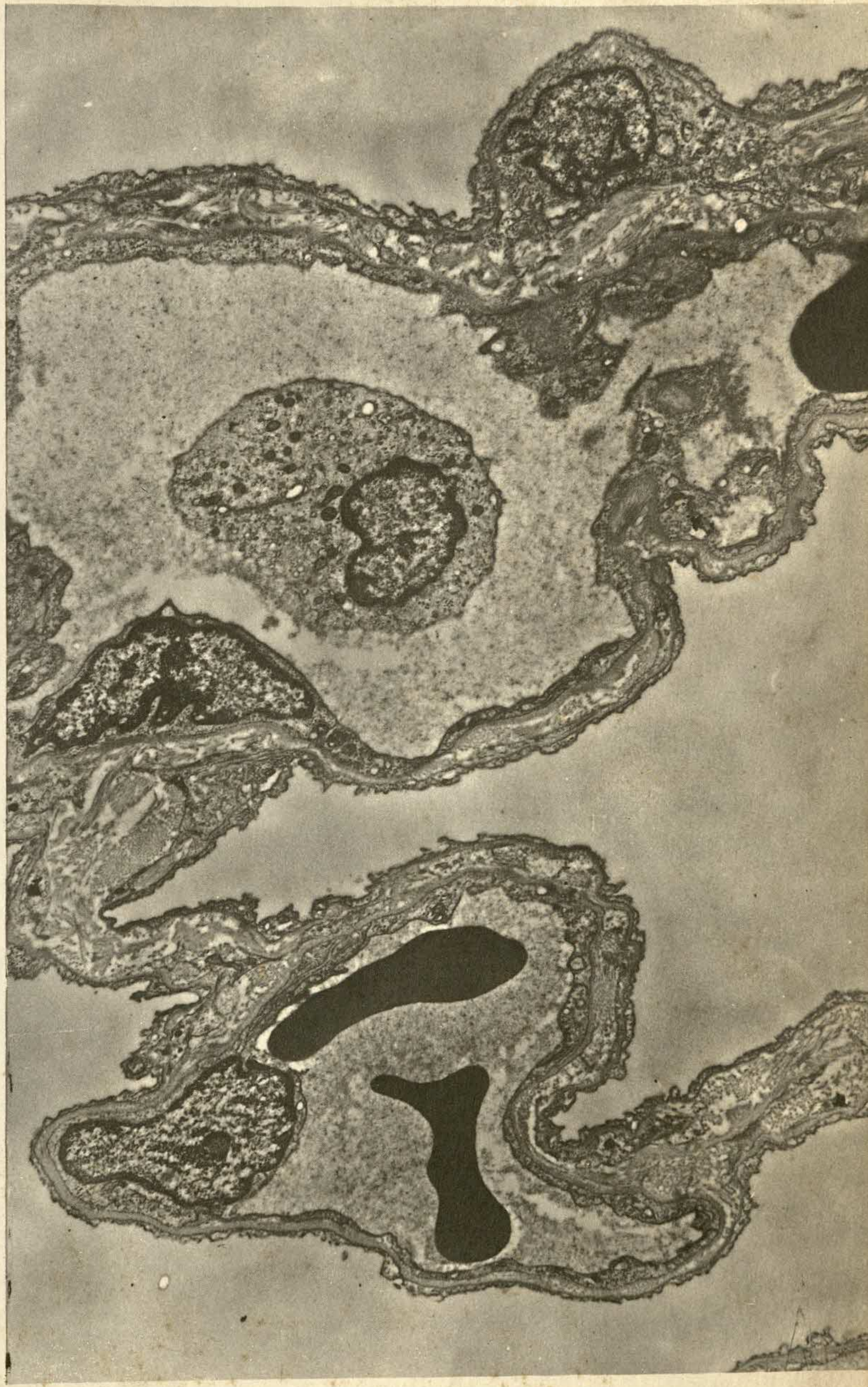
## *The respiratory function of the blood*

Oxygen which has succeeded in passing through the wall of the alveoli dissolves in the plasma, but because of the limited solubility of oxygen only a very small quantity passes in this form, actually only about 5 cc of oxygen per litre of blood. On the other hand, blood contains haemoglobin, a protein which forms the main part of the erythrocytes and which is capable of combining in unstable fashion with oxygen in the proportion of 1·34 cc of oxygen per gram of haemoglobin. Since 1 litre of blood contains 150 grams of haemoglobin, it becomes capable of transporting 200 cc of oxygen, of which only 5 cc are in solution. The chemical reaction between oxygen and haemoglobin can be represented thus:

$$Hb + O_2 \rightleftharpoons HbO_2$$

When $O_2$ is abundant, the reaction takes place from left to right and more oxyhaemoglobin, $HbO_2$, is formed. If, on the contrary, oxygen is lacking in the tissues, which are constantly using it, the reaction moves from right to left and oxygen is liberated. This mechanism is described quantitatively by the curve of the dissociation of oxyhaemoglobin in the blood (fig. 3). This figure also shows the effect of carbon dioxide on the dissociation curve: if the pressure of carbon dioxide increases, the affinity of haemoglobin for oxygen is decreased. Thus the passage of oxygen within the tissues from the blood to the cells is

*Fig. 5. Photograph taken by an electron microscope of the alveolar wall of the lung. (Mag. × 8,000. Reproduced by permission of the Laboratoire du Centre d'Etudes et de Recherches des Charbonnayes de France).*



facilitated. About 10 per cent of the carbon dioxide in blood is present as dissolved gas, and 25 per cent is combined with haemoglobin; the other 65 per cent consists of carbonic acid which is almost entirely dissociated into bicarbonate ions, $HCO_3^-$, and hydrogen ions, $H^+$. The higher the partial pressure of carbon dioxide, the more of it the blood fixes.

The hydration of carbon dioxide to form carbonic acid is a very slow phenomenon, too slow for the needs of higher organisms. In the red corpuscles, into which the major portion of the carbon dioxide diffuses, its transformation is catalyzed by an enzyme called carbonic anhydrase and the following reaction takes place:

$$CO_2 + H_2O \overset{\text{carbonic anhydrase}}{\rightleftharpoons} H_2CO_3$$

$$\text{then } H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

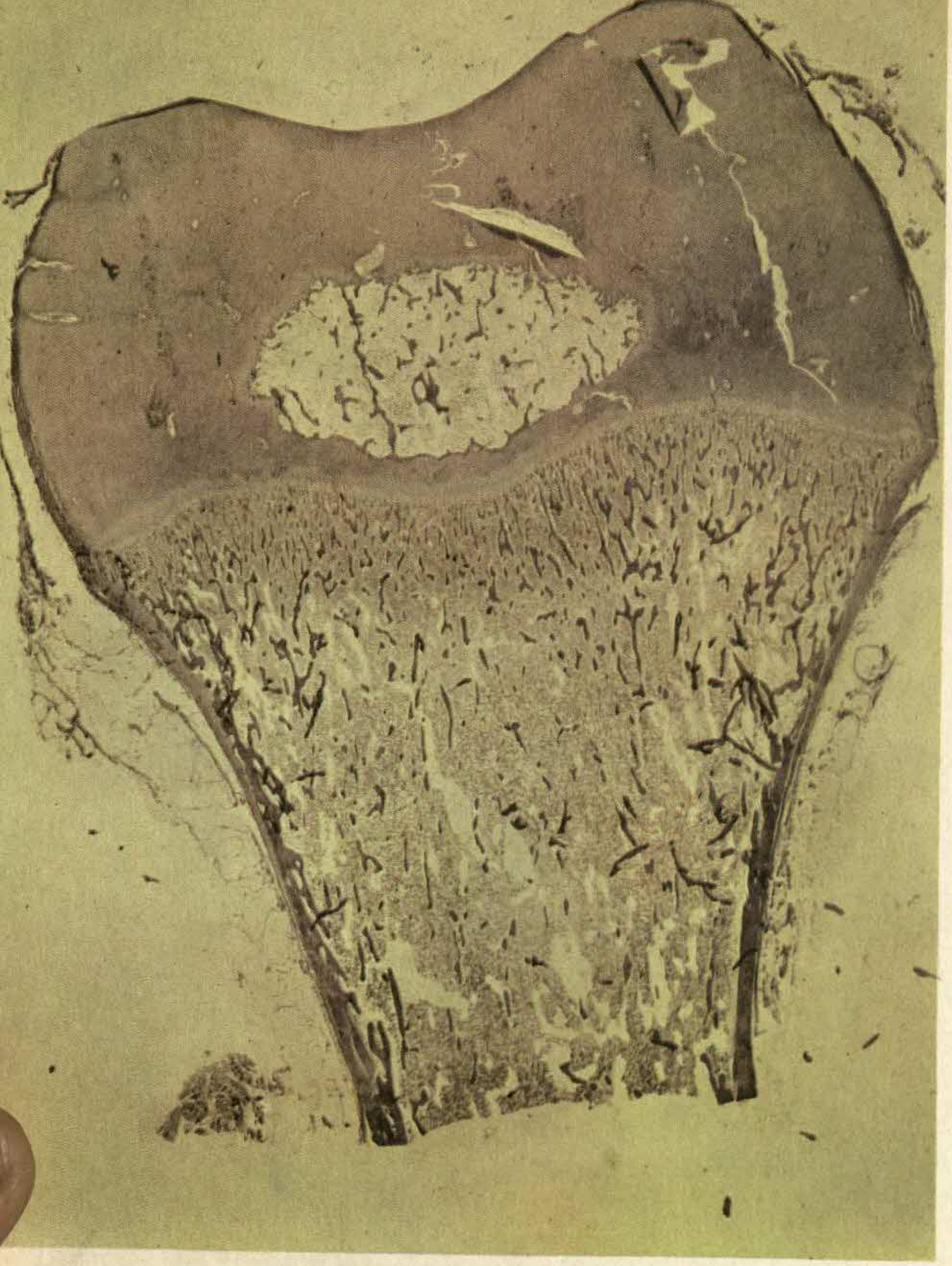
Figs. 3 and 4 show that if the blood loses 50 cc of oxygen, the partial pressure of oxygen is reduced by about 60 mm Hg, but the rise in carbon dioxide content in the blood leads to an increase of only 5 to 6 mm Hg. That is why the total pressure of the gases in the venous blood is always well below that of the atmospheric pressure, and lower than the sum of the partial pressures of all the gases contained in the arterial blood (table 1).

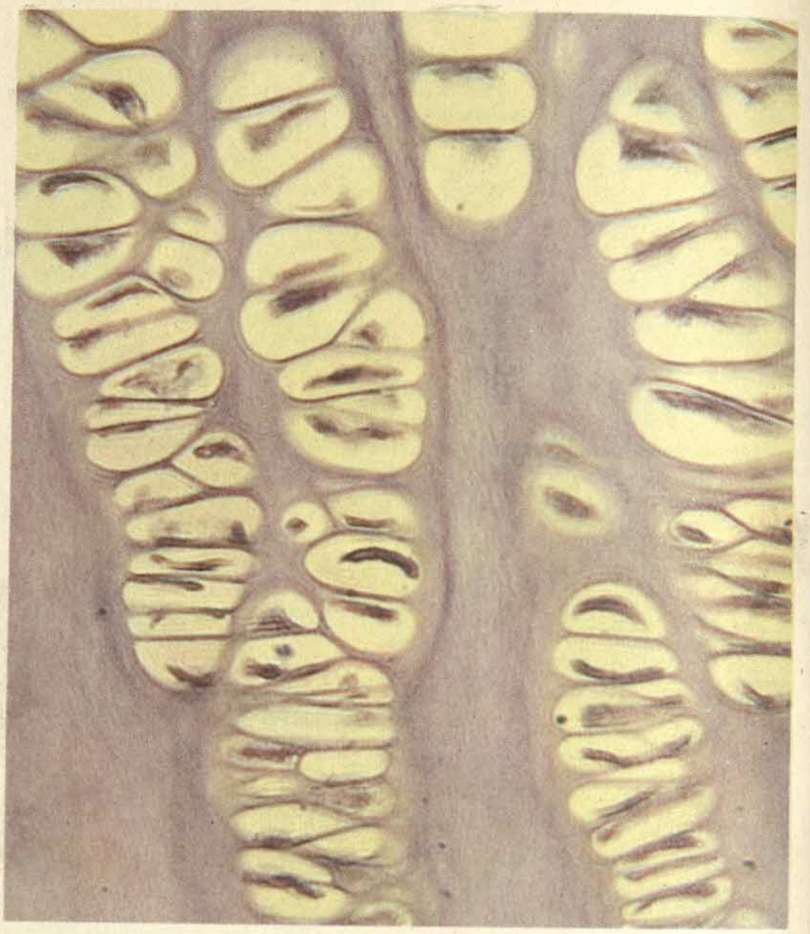
Table 1

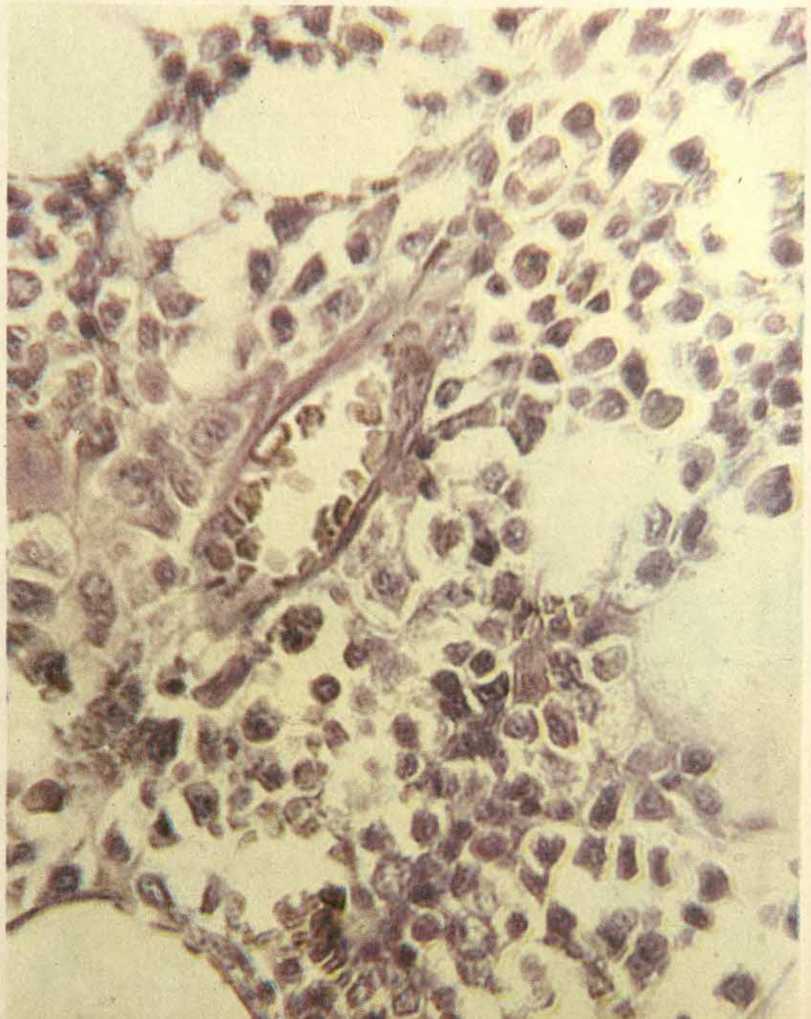
| | $P_{O_2}$ | $P_{CO_2}$ | $P_{N_2}$ | $P_{H_2O}$ | Total |
|---|---|---|---|---|---|
| Atmospheric air | 158 | 0·3 | 596 | 5·7 | 760 |
| Air in the trachea | 150 | 0·3 | 563 | 47 | 760 |
| Expired air | 116 | 32 | 565 | 47 | 760 |
| Alveolar air | 100 | 40 | 573 | 47 | 760 |
| Arterial blood | 95 | 40 | 573 | 47 | 755 |
| Mixed venous blood | 40 | 46 | 573 | 47 | 706 |
| Tissues | 25 | 50 | 573 | 47 | 695 |

This explains why, when a gaseous cavity is formed within the organism, for instance, an extravasation of air in the pleural cavity (pneumothorax) or elsewhere, this air at a pressure necessarily close to atmospheric pressure is reabsorbed more or less rapidly into the venous blood where the pressure is lower.

The exchange of gases at the level of the capillaries of the tissues follows a path very similar to that described for the pulmonary capillaries. The phenomena of cellular respiration will be described in another chapter.







# Bone and cartilage

*Among the more important tissues that make up the human body, the supporting tissues are bone and cartilage, as opposed to the vascular, respiratory, or digestive systems. Above, a section through the head of a long bone. It is composed of spongy bone containing red marrow and a cavity containing yellow fatty marrow. A thin layer of cartilage can be seen separating the head of the bone from the shaft. Above to the right, a section through cartilage, highly magnified. The cartilage cells (chondrocytes) can be seen developing from the top downwards in their lacunae. Bottom right, a section through bone marrow; this is where the cellular elements of the blood are produced. (Preparations by A. Mazabrand, Photo Lod).*

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# The kidney

### *Jean HAMBURGER*

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It has long been known that the kidney does not manufacture fully the elements which compose the urine. It serves only to extract them unchanged from the blood plasma where, with very few exceptions, they already exist. In other words, the urinary function is one of excretion, but the kidney exercises a choice among the numerous organic or mineral substances present in the circulating blood. Some substances, such as the proteins, are wholly retained in the organism, although the blood plasma contains a high concentration of them (70 to 80 grams per litre). Others, on the contrary, are entirely taken away by the kidney and eliminated through the urine: this is the case with certain foreign bodies such as penicillin or streptomycin, which the organism eliminates by means of the kidney until no trace of them remains in the circulating blood. Between these two extremes, most of the constituents of the plasma are excreted in the urine in variable proportions; the quantities thus taken away by the kidney are not fixed and vary even from day to day for each substance eliminated. Keeping the concentration and reserves of these substances constant within the organism seems to call forth an incredibly subtle response in each of the quantities excreted. Whether the amount of salt absorbed is very great or very small, the concentration of salt in the blood and the total amount of salt in the individual will not vary at all: if practically no salt is absorbed, no salt will be eliminated; if much salt is absorbed its rate of elimination will rise, until after a few days it exactly counterbalances the excess taken in; the quantity of salt taken away by the kidney will be precisely equal to the excess received. If we reflect that the amount of each of the innumerable substances excreted every day in the urine is also well adjusted, we can perceive what an admirable instrument the kidney is and how intricate the network of information (or of 'feedbacks' in the language of cybernetics) that it possesses. Finally, we ask ourselves what internal device is capable of varying at every moment the rate at which each constituent of the blood plasma is taken away by the kidney.

## *The nephron*

The basic instrument of this mechanism is the nephron. Each kidney is formed of the assembly of about a million nephrons, joined by an interstitial tissue through which the blood vessels and nerves pass. Thus the nephron is the morphological and functional unit of the system determining the composition of the urine. Its structure is very strange and until recently has been a most intriguing puzzle for physiologists (fig. 1).

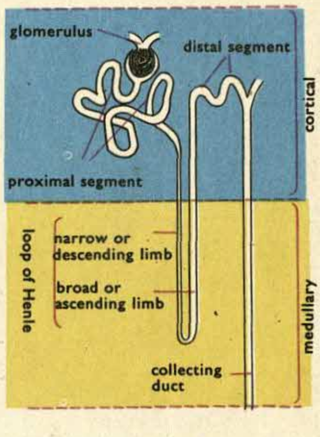

*Fig. 1. Structure of the nephron.*

Imagine first a small vermicular bundle of arterial capillaries, placed between the afferent arteriole by which blood arrives and the efferent arteriole by which it leaves; this capillary network, enclosed in a small round capsule, is the glomerulus which forms the head of the nephrôn. Although the glomeruli are so small as to be hardly distinguishable by the naked eye, in a kidney section the total quantity of blood which passes through them every minute is enormous: over a litre for the two kidneys of an adult, which is a quarter of the total distributed to all the rest of the organism in the same time.

Leading from the glomerulus, the uriniferous tube is a long duct which pursues a sinuous course, often folded back on itself; its total length is approximately 20 mm; it includes a first segment, the 'proximal segment' or 'convoluted tube', the lumen of which is lined with large cylindrical cells that show all the morphological characteristics of a high degree of differentiation; then comes the 'loop of Henle' (like a hairpin); then the 'distal segment' which finally joins a system of collecting tubes through which the urine will pass into the excretory cavities.

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A device so curious in form could not fail to excite the imagination of the theorizers. At a time when doctors thought they were entitled to express authoritative opinions on

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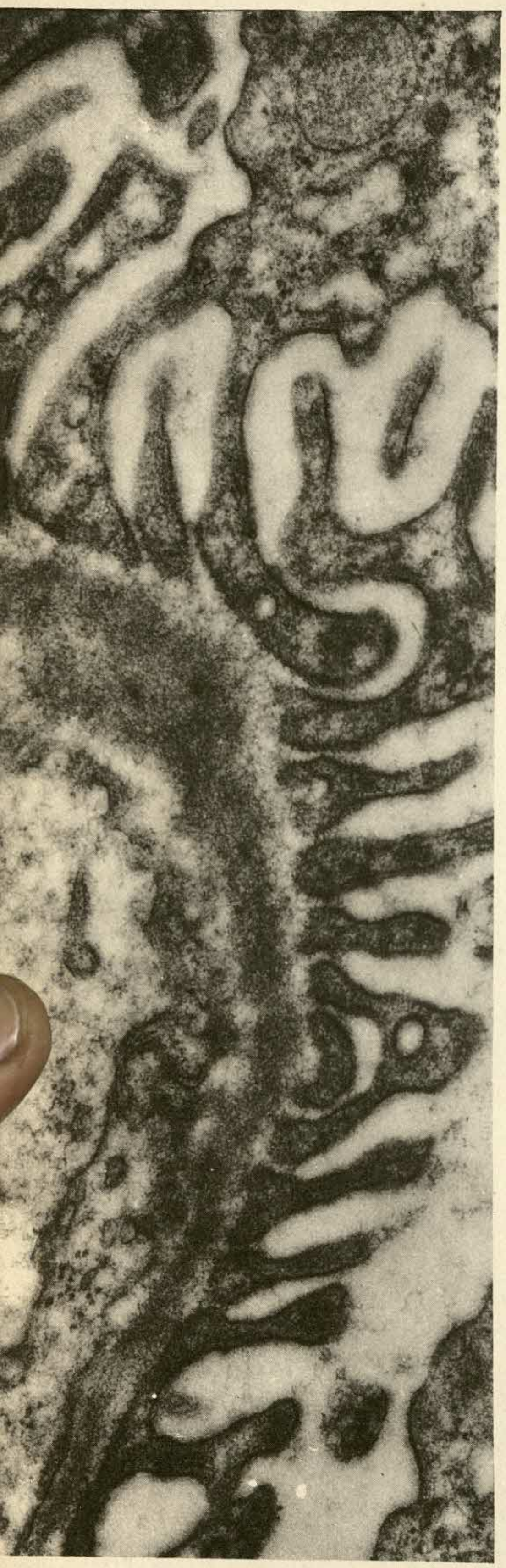


*Fig. 2. Wall of a glomerular capillary, basal membrane, pedicels of the epithelial cells. (Electron Microscopy Laboratory of Professor Hamburger. Mag. × 50,000).*

all sorts of topics, but whose beliefs could not be supported by any serious demonstration, innumerable systems were constructed to explain how the nephron produced urine. The history of the endless discussions that raged for almost a century is the most remarkable example of the extreme confusion caused by a lack of scientific method in medicine. The reader will be spared an account of these sterile discussions, so as to give straight away the solution to this enigma, as it appeared clearly when sufficient accurate experimental data had at last been accumulated. The solution resulted from two types of observation process. On the one hand, Richards and his successors in Philadelphia had the boldness to extract, with the aid of micropipettes directed under considerable enlargement, the fluid contained in the lumen of the nephron from the kidney of living animals, at different stages. Chemical analysis by microtechniques of the fluid obtained showed for the first time the successive stages in the formation of urine between the glomerulus and the final collecting tube. On the other hand, Rehberg in Scandinavia, and then Homer Smith in New York, showed that certain test substances obey such characteristic rules of elimination by the kidney that a whole series of inescapable consequences concerning the intimate mechanism of urine formation can be drawn from them. But this is to anticipate. First we should obtain an overall picture of the functioning of the nephron.

## *Glomerular filtration*

The capillaries of the glomerulus first allow a considerable fraction of the blood plasma to filter through their wall membrane. About one-fifth of the plasma thus filtered passes from the circulating blood flow into the uriniferous tube: a large volume, since it represents 120 ml of filtrate per minute for the two kidneys of an adult, or over 170 litres in 24 hours. This enormous amount of crude urine poured by the glomeruli into the proximal tube has all the characteristics of an ultra-filtrate of the blood plasma: the bulky protein and fat molecules of the plasma have been stopped by the capillary wall, but all the other dissolved substances pass through with the water, and their concentration in the crude urine is identical to that in the blood plasma. This is the first stage in the production of urine, and is known as *glomerular filtration*; the 170 litres of initial fluid thus filtered every day are subjected during their tubular passage to a process of concentration, of reduction in volume, and finally of revision of the strength of each dissolved substance. This delicate and precise operation will finally lead at the other end of the tubes to the production of 1½ litres of urine, in which the concentration of each constituent will be exactly adjusted to the required value.

## *Tubular reabsorption*

The main activity of the uriniferous tube is, therefore, one of reabsorption. Ninety-nine per cent of the water filtered by the glomerulus is reabsorbed by the tubular cells and returned to the blood circulation; the final volume of urine will not exceed 1 per cent of the volume of the original material to be treated by the tubules. Certain dissolved substances are even completely reabsorbed by the tubular cells and no trace of them will be left in the final urinary secretion. Among these is blood sugar or glucose, of which there is 1 gram per litre in the glomerular filtrate, as in the blood plasma, and which does not appear at all in normal urine. It may seem a strange complication of nature to filter 170 grams of blood glucose every day to no purpose, only to return it to the same blood without having done anything with it. But this very mechanism which appears pointless under normal conditions is a most precise system of elimination. As soon as the concentration of glucose in the blood significantly exceeds the physiological norm, the tubular reabsorption is stopped by the abundance of filtered glucose and the excess is not reabsorbed. The excess is eliminated from the organism in the resulting urine. This example shows clearly the ingenious system of filtration and reabsorption which controls the formation of urine. There exists a limit for the tubular capacity of reabsorption with regard to most substances, so that any excess in the blood, over and above a certain concentration, will be eliminated. Inversely, a fall in the concentration of the substance in the blood plasma and therefore in the glomerular filtrate will result in complete or almost complete reabsorption, and none of the constituents of the blood whose concentration was falling dangerously will be lost. Thus the precise regulation of tubular reabsorption ensures a constant blood composition.

This primary control would be insufficient, however, and would still allow excessive fluctuations in the concentration of the principal constituents of the blood plasma. As so often happens in an organism where a series of distinct systems converge and overlap in controlling a single function, the regulation of tubular reabsorption depends on a number of mechanisms which complement and balance each other. The most important of these are humoral, the functioning of the cells of the renal tubes being regulated by hormones secreted by various glands, especially the posterior lobe of the pituitary and the cortical region of the suprarenal glands.

The posterior pituitary gland releases into the blood a hormone specifically capable of increasing the reabsorption of water: this is pitressin, which is so active that 1/10,000th of a ml of ordinary posterior pituitary extract in circulation (10 units per ml) is sufficient to increase noticeably the tubular reabsorption of water in a man who has drunk a quantity of it. In other words, it decreases diuresis, ie, the rate of production of urine. So active a hormone is capable of playing an important role in controlling the quantity of water eliminated each day in the urine; its secretion is indeed determined by the water concentration of the blood plasma, or more exactly by its osmotic pressure. Thus the slightest tendency to an excess of water stimulates the liberation of pitressin which at once reduces the urinary losses of the precious fluid, by stimulating its reabsorption by the renal tubes to the maximum. The perfection of this regulatory mechanism, as was emphasized by the English physiologist Verney, will be realized from the fact that a variation of the order of 1 per cent in osmotic pressure provokes changes in the excretion of water, by about 1,000 per cent, through the action of the pituitary antidiuretic hormone. Thus the osmotic pressure of the internal medium is maintained with constancy.

The suprarenal cortex provides another example of these extraordinary systems of information and control which regulate, from a distance, the activity of the kidney cells. In this case the reabsorption of salt, sodium chloride, is closely controlled by several suprarenal hormones, especially aldosterone which specifically stimulates the reabsorption of chlorine and of sodium by the kidney.

These control mechanisms are closely intertwined, so that all the scientist's skill is required to unravel the tangle little by little. Thus the reabsorption of salt, which has just been mentioned, directly influences the reabsorption of water, for this always obeys the fundamental law of osmosis, and every movement of salt in the organism automatically brings about a redistribution of water. Thus an increase in the reabsorption of salt also increases the reabsorption of water; a decrease reduces it. For example, a concentrated salt solution injected intravenously immediately increases the quantity of salt which escapes reabsorption by the kidney, and as an immediate consequence it increases the volume of water also unreabsorbed. Consequently the flow of urine rises greatly. This reaction is usually known as osmotic diuresis. This illustrates the complex equilibria which seem to be the special feature of physiological mechanisms; as explained above, any increase in the osmotic pressure of the blood plasma brings about a decreased elimination of urine through pituitary secretion, on the one hand, and on the other, an increase of this same elimination by means of osmotic diuresis. Thus balanced between many opposing influences, and directed by an invisible extrinsic system, the functioning of the kidney is a model of unusual perfection for anyone who seeks to understand the homoeostatic mechanisms of life.

## Tubular excretion

More recently the picture of the production of urine by filtration and reabsorption has been complicated by the discovery of a third activity which is involved in determining the final composition of urine: this is the process of tubular excretion. The renal tube is capable not only of reabsorbing and returning to the blood some of the substances which have filtered into the tubular lumen, but also of functioning in the opposite direction and extracting certain substances from the circulating blood. These it passes to the crude urine, thus adding more of these substances to the amount already filtered by the glomerulus. The activity of the tubular cells is, therefore, astonishingly complex, and transport takes place simultaneously in both directions between the lumen of the tube which borders them on the inside and the blood plasma which bathes them on the outside. The quantity and the direction of transfer are specifically and rigorously controlled for each substance to be eliminated. It is even more amazing that this applies also to artificial substances invented by man for the purpose of exploration or treatment and thus never before encountered by the tubular cells in their contacts with the natural media. Indeed, many substances eliminated by the tube without being reabsorbed are synthetic organic products, foreign to the organism and introduced into the blood by intravenous injection: the best studied examples are phenol red (a dye used to test the functional condition of the kidneys), the 3·5 di-iodo-4-pyridon-N-acetate

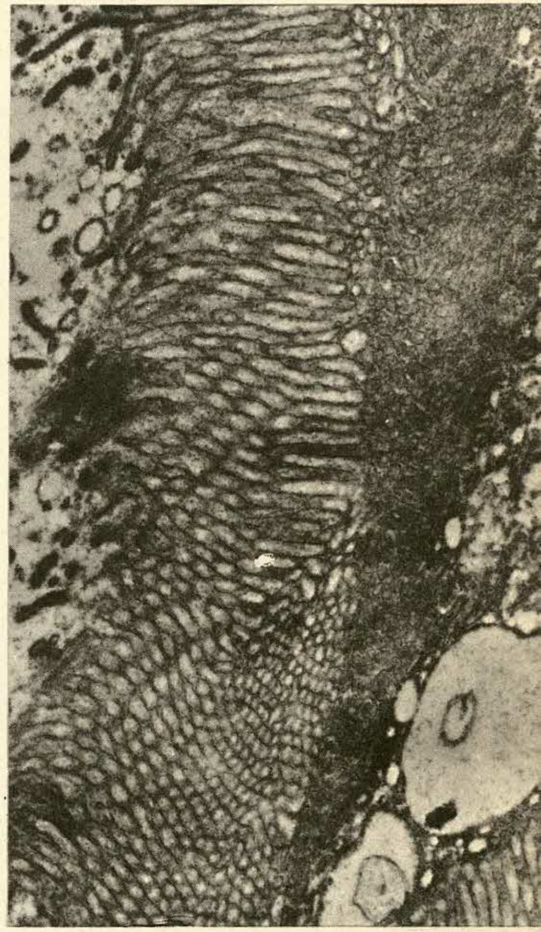


*Fig. 3. Brush border of a proximal tube. The villosities of the brush are seen to be horizontal; the lumen of the tube is visible on the left. (Laboratory of Professor Hamburger. Mag. × 50,000).*

of di-ethanolamine (an iodine compound often used to make the urinary cavities opaque for radiography by x-rays), para-aminohippuric acid, penicillin, streptomycin. It is today possible to measure with great precision the quantity of each of these substances eliminated by glomerular filtration and the quantity added thereto by tubular excretion.

How has such precision been reached? By what means is it possible to separate so clearly the substances reabsorbed by the tubes from those eliminated by them? The story is worth telling, for it is one of the most successful exploits of physiology in the past few years.

## The concept of clearance

The story starts from the time when it was discovered that certain substances, although quite different in nature, showed the same singular behaviour in urinary elimination. To understand this, it must be remembered that if twenty constituents of the blood plasma are taken at random—for example, urea, uric acid, chloride, sodium or potassium ions, vitamins, amino acids, or even substances temporarily and artificially introduced into the plasma, such as medicines—no two of them are eliminated by the kidney to the same extent and with the same rapidity. To try to express this idea more precisely, a coefficient of urinary excretion can be established for each of these substances, by comparing their urinary output (the amount eliminated in the urine per minute) with their concentration in the blood plasma. This ratio is generally known as the clearance of the substance studied.

The clearances of the various constituents of plasma are all different from one another and apparently unpredictable; these variations may be exemplified by clearances varying from 0 (for substances, such as glucose, which are not normally eliminated in urine) to 600 or 700 (for the iodine compounds used in urography, and para-aminohippuric acid), including such diverse figures as 2 or 3 (for chloride or sodium ions), 75 (urea), 400 (phenol red). Moreover, the clearance of a given substance varies with its concentration in the plasma: for substances with a low clearance, it increases as their concentration in the plasma increases; for substances with a high clearance the opposite occurs.

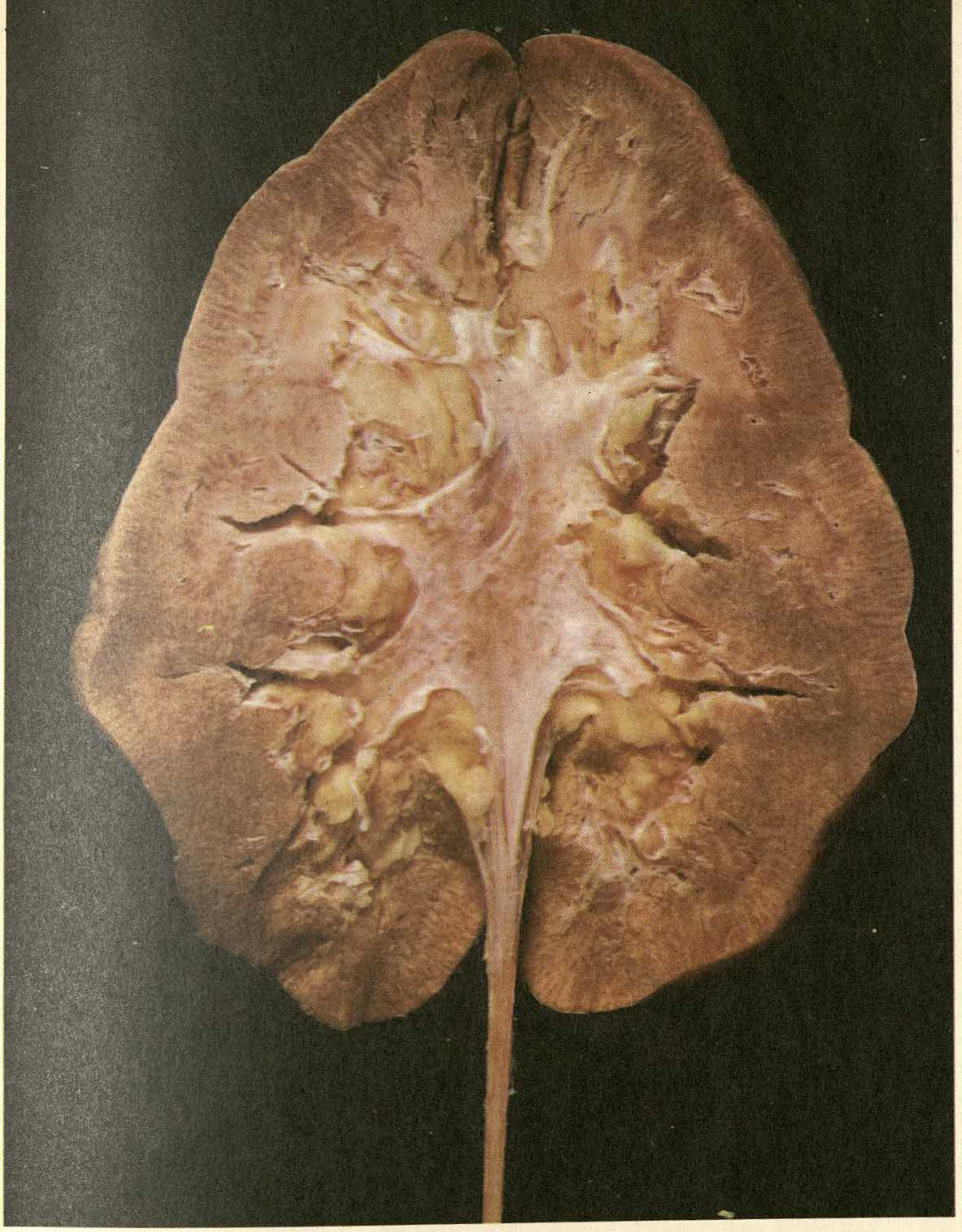
Let us go back now to those particular substances whose strange behaviour was introduced above. These substances are inulin, mannitol, sodium thiosulphate, endogenous creatinine, sodium ferrocyanide, acetylsulphamide, allantoin, etc, considerably varied substances which apparently have no common feature, either chemical or biological. All these unusual substances, however, have an identical urinary clearance of 120 in a healthy adult. Moreover, in contrast to the general rule, this clearance is constant and does not vary as the concentration in the blood varies. In other words, whatever the amount of any of these substances contained in 1 ml of blood plasma, the amount eliminated by the kidneys in one minute is always 120 times higher. Such constancy is surprising, especially when shared by such different substances.

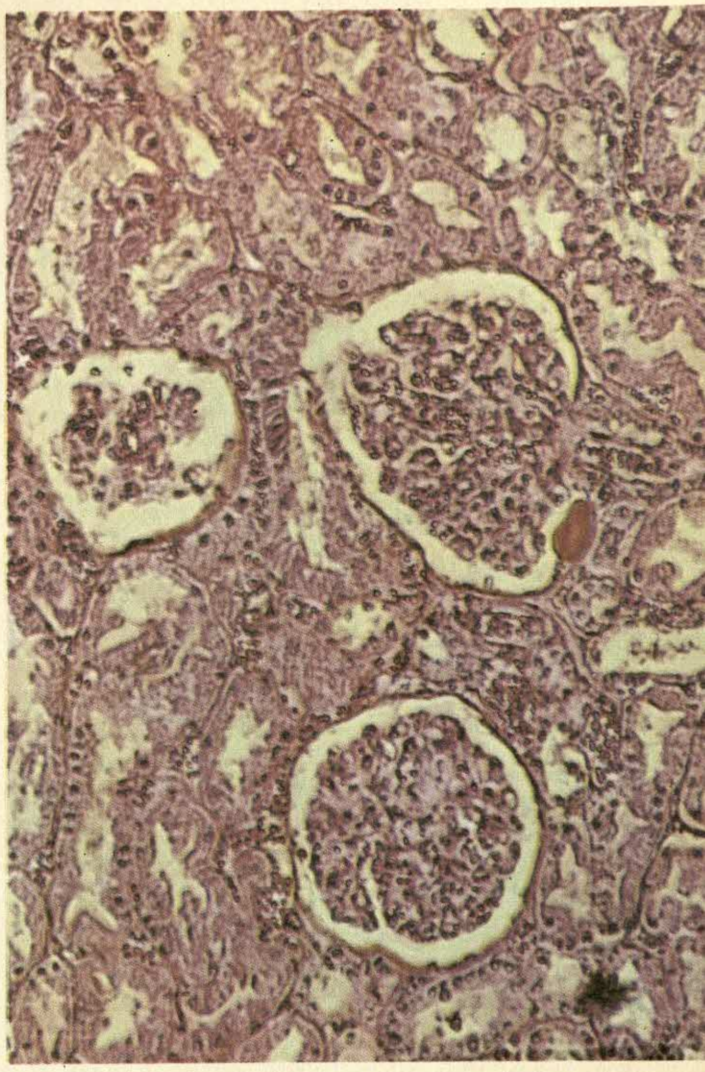
The key to the puzzle is nevertheless simple. All these substances have one characteristic in common: they are eliminated simply by glomerular filtration. Once they have passed the glomerular filter, their concentration is unchanged as they pass the lumen of the tube; for they undergo no tubular reabsorption or excretion. It is easy then to understand why they all have the same coefficient of excretion: the process of concentration of all these substances is in fact identical, and it takes place by the interplay of the reabsorption of part of the water in which they are dissolved. Without the agency of the tubular reabsorption of water, how could it be explained that the concentration index of such different bodies is exactly the same? There are many other arguments in favour of this point of view. Suffice it to say that the substances eliminated by glomerular filtration alone—that is by a mechanism similar to the purely physical processes of ultra-filtration—pass into the crude urine at a concentration identical with the concentration in the plasma, whatever this may be, so that it is easy to understand why their clearance is independent of their concentration in the blood plasma. For substances which are subjected to tubular activity this is not the case, because, as we shall see later, this is an activity which is easily exhausted and may even reach its limits as soon as the concentrations are high.

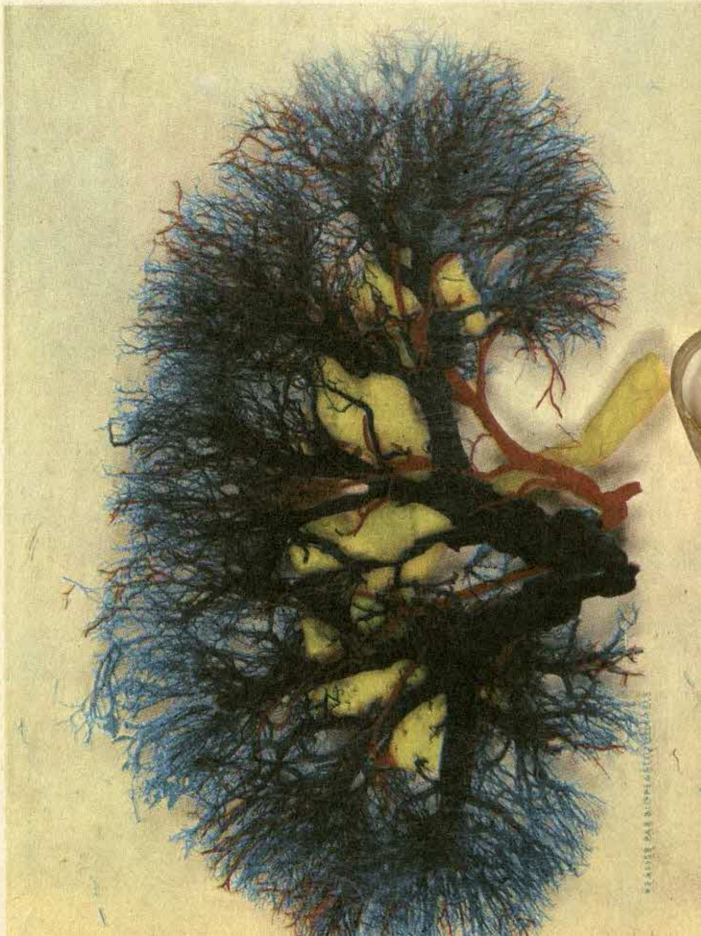
## The measurement of filtration

There are, therefore, a number of substances which are eliminated by the glomeruli alone and are unaffected by the tubular cells. The immediate importance of this is to allow a precise quantitative estimate of glomerular activity. The plasma clearance of these bodies is 120; in other words, 120 times the amount found in 1 ml of glomerular filtrate (or plasma, which amounts to the same thing) is found in the final urine every minute, so that the volume of this filtrate must have been

(1) *The argument outlined in this way contains a weakness; it happens that some of the filtered substances are first reabsorbed, then excreted again a little lower down. Thus it can almost be taken for certain, following the distinguished work of Morel and the French school, that one of the essential constituents of the organism, potassium, undergoes total reabsorption, and the fraction finally eliminated in the urine comes entirely from tubular excretion. One is thus forced to admit that a substance with a clearance less than the glomerular clearance may nevertheless be eliminated very well by tubular excretion.*







# The kidney

*Above: a section through the kidney, opened along its plane of symmetry. Several calyces are seen converging towards the pelvis, (centre). They collect the urine, which is taken to the bladder through a duct called the ureter. Top right: histological section of kidney tissue. Several characteristic glomeruli may be seen. Right: a model of the muscular and excretory systems of the kidney: in red, the arterial system: in blue, the venous system; in yellow, the pelvis and the calyces. This model was made by injecting plastic materials of different colours into the veins, the renal arteries, and the ureter; the kidney was then immersed in an acid which, by destroying the 'organic mould', revealed the admirable cast seen in this photograph. (Photo Lod. The two upper photographs were taken in the department of Professor Kourilsky, Hôpital Saint-Antoine, Paris. Preparation by Madeleine Russon).*

120 ml per minute. The measurement found of the clearance of such substances as inulin or mannitol is nothing less than a measure of the volume of glomerular ultra-filtrate, and by simply comparing two titrations, one in the blood and one in the urine, it is possible to know the number of ml of plasma filtered by the glomeruli of the two kidneys of a man.

There is more to it than this. The figure of 120 ml per minute measures not only the glomerular filtration, but also the other types of renal elimination. The output of the substances partially reabsorbed by the tube will be reduced by a corresponding fraction and consequently their clearance will be less than 120; the more effective the reabsorption, the lower the clearance. If, on the contrary, the clearance of a substance is higher than 120, it can be inferred that the tubular cells add a certain amount to that already filtered by the glomeruli; in other words, this substance undergoes no tubular reabsorption, but, on the contrary, tubular excretion. Therefore, para-aminohippuric acid, whose clearance with a low plasma concentration is about 600 to 700 ml per minute, must be eliminated partly by glomerular filtration (a portion equal to 120 ml per minute) and the rest (over four-fifths) by strong tubular excretion.[1]

## Limits of tubular activity

Tubular activity, whether reabsorption or excretion, appears on analysis to be quite different from glomerular activity. The characteristics of the latter, as mentioned above, are similar to those of the simple physical processes of filtration. The former, on the contrary, has all the features of a highly specialized process, depending on very complex systems of transfer by means of enzymes and requiring a high expenditure of energy in order to function. These systems resemble those encountered when studying the various secretory cells of the body. This distinction accounts for limitations in the functioning of the tubular system which are unknown to the glomerular system. When the concentration of substances to be reabsorbed or excreted exceeds a certain level, the tubular cells reach a limit to their activity, which can be measured and used to evaluate the size and condition of the tubular systems in a living individual.[2] Likewise, when the simultaneous elimination of different substances is being studied, the strange phenomena of tubular competition are encountered. In this the action of the tubular cells on one of these substances is restricted when they are engaged in eliminating or reabsorbing another substance (probably using the same enzyme system for trans-cellular transfer).

It has thus been possible to analyze the behaviour of the nephron in the most accurate and detailed way, undoubtedly because the kidney is a privileged organ and the experimenter is able at every moment, and without causing any damage, to know what reaches it (simply by a blood test) and what leaves it (by collecting the urine).

## Measurement of the renal blood flow

The efforts of research workers have been rewarded by finally being able to measure in the living human subject the quantity of blood which flows through the kidneys in unit time. To arrive at this, a chemical titration in the blood and in the urine are sufficient. The principle is simple: it has been said above that certain substances such as para-aminohippuric acid have a surprisingly high coefficient of excretion, since their clearance reaches 600 to 700 ml per minute (for sufficiently low concentrations in the plasma). It has been demonstrated, by direct blood tests on the renal veins, that such an elevated excretion corresponds to almost total (within 10 per cent) extraction of the acid from the blood flowing through the kidney. Consequently, in the outgoing vein there is practically no para-aminohippuric acid left. It has been completely eliminated in the urine right away. By measuring the clearance of this acid we can see that urine eliminates each minute 600 times the quantity contained in 1 ml of plasma; since this output equals all the acid which reached the kidneys during the same minute, it follows that the volume of blood plasma which passed through the kidneys during that time was exactly 600 ml. Thus, simply by measuring the clearance of para-aminohippuric acid at a low plasma concentration, it can be shown that 600 ml of plasma, or 1,200 ml of whole blood, flow through the kidneys of a normal adult every minute.

## An energy-saving system

The reader who has followed this account so far may be tempted to ask the following question: how does this scheme, admirable though it may be, account for the strange form of the tubes? In particular, of what use is the hairpin course, in which the uriniferous tube suddenly plunges towards the depth of the kidney, and then returns in the opposite direction along the upward branch? The

(2) *It is because of this limit to the tubular activity that the clearance of most substances varies when their plasmatic concentration varies. In the case of the substances reabsorbed by the tubes, the reabsorbed fraction reaches a maximum, above a certain concentration, whereas the fraction filtered by the glomeruli goes on increasing in proportion to the concentration in the plasma. Finally, the fraction reabsorbed becomes negligible compared with the fraction filtered, so that the clearance increases and tends to reach the figure of 120, which is the clearance of substances exclusively eliminated by glomerular filtration. For an identical reason, the substances excreted by the tubes have a clearance which is lowered beyond a certain plasmatic concentration, and here again tends towards the degree of clearance of substances exclusively filtered. This accounts for the fact, at first sight inexplicable, that low clearances rise and high ones fall, when the concentration in the blood plasma of the substance studied rises.*

(3) *In fact, this over-simplification of the theory of Wirz gives only a rough idea of its importance, but it is certain that his theory marks a significant and indeed revolutionary step forward in the fundamental understanding of the physiology of the kidney.*

answer to this question has been known for several years, thanks to the Swiss scientist, Wirz, and some others. It is known today that this system within the kidney serves to save energy. It should be realized that the permanent transfer of the large amount of substance involved in the filtration–reabsorption mechanism represents an enormous expenditure of energy for the tubular cells. This expenditure is reduced to a reasonable level because the kidney profits by a system sometimes used in industry, called the 'multiplying countercurrent system'.

The principle of this system is that short-circuits occur through the membranes and the interstitial fluid separating the upward and the downward branches of the loop. Through these short-circuits the composition of the urine already flowing in the upward branch influences to a certain extent the composition of the urine which is still in the downward segment of its passage; so the urine acquires in advance the composition to which it must tend and little energy will be needed to initiate, carry on and complete the change to the final urine.[3]

## *The responsibility of the kidney in the constancy of the internal environment*

Equipped as it is for the elaboration of a urine of variable composition, the kidney is capable of assuming a major responsibility in the organism; that is, of keeping the composition of the internal environment constant.

Reading again the pages in which Claude Bernard first defined the 'internal environment', one cannot fail to admire the extraordinary foresight of the author of the *Introduction à la médecine expérimentale*.

All subsequent data have but confirmed this fundamental concept that the tissues of the organism are not directly linked to the external environment but live in an aqueous internal medium, which fills the intercellular spaces and maintains a remarkably constant physico-chemical composition. This is true no matter how varied may be the conditions of the environment in which the individual finds himself. This internal environment, or as it may be called, the extracellular fluid, is responsible for all communication between the outside world and the cells of the organism; it acts as a shock-absorber and it protects them from all disturbance in the environment which they would be incapable of resisting. The individual may be regarded as a colony of innumerable cellular elements, fragile and specialized, which would die at once if the fluid which surrounds and links them altered for one single moment its pH, its osmotic pressure, its content of oxygen, or any of its main chemical constituents.

The constancy of the internal environment depends at least to 75 per cent on the kidney. This is no mean task, for every day the most varied and sometimes the most unexpected substances are taken from the outside into the ten or fifteen litres of an adult's extracellular fluid (a quarter of this forms the circulating blood plasma, and the rest the interstitial fluids and the lymph): one day a person may drink a large amount, the next day he may absorb only a half or a quarter of the previous day's intake; one week his food may be very salty, but the next week his food may be almost without salt, depending on the whim of a cook or the exigencies of locality. From one individual to another the differences are even greater: one person eats like a horse, another just pecks at his food; one fills himself with acid foods, whereas the other swallows quantities of alkaline medicines to cure his gastric troubles. One follows a doctor's prescription and absorbs every day more calcium than is contained in the whole of his extracellular fluid; another has for years been taking enormous doses of an iodine preparation; a third believes in the virtue of vitamins and swallows ten times more fruit juice or ascorbic acid than does his neighbour. Yet in all these individuals the alkalinity and the concentration of calcium, iodine or ascorbic acid of the internal environment remain quite unalterable. The kidney retains or eliminates just enough of each substance to prevent, to the extreme limit of its capabilities, any appreciable modification of the composition of the blood and of all extracellular fluid.

So far, only the intake from the outside has been taken into account. Living cells also pour a large quantity of different substances and waste products into the internal environment every day, as though it were some huge dump; these would soon accumulate in the fluids and disturb the whole balance if here again the kidney did not keep order.

Physiologically, therefore, the kidney must not be regarded as just an organ for the formation of urine, or as a simple apparatus to rid the body of its waste products. The kidney is the guardian of the internal equilibrium, and the chief controller of the delicate chemical balance necessary for life.

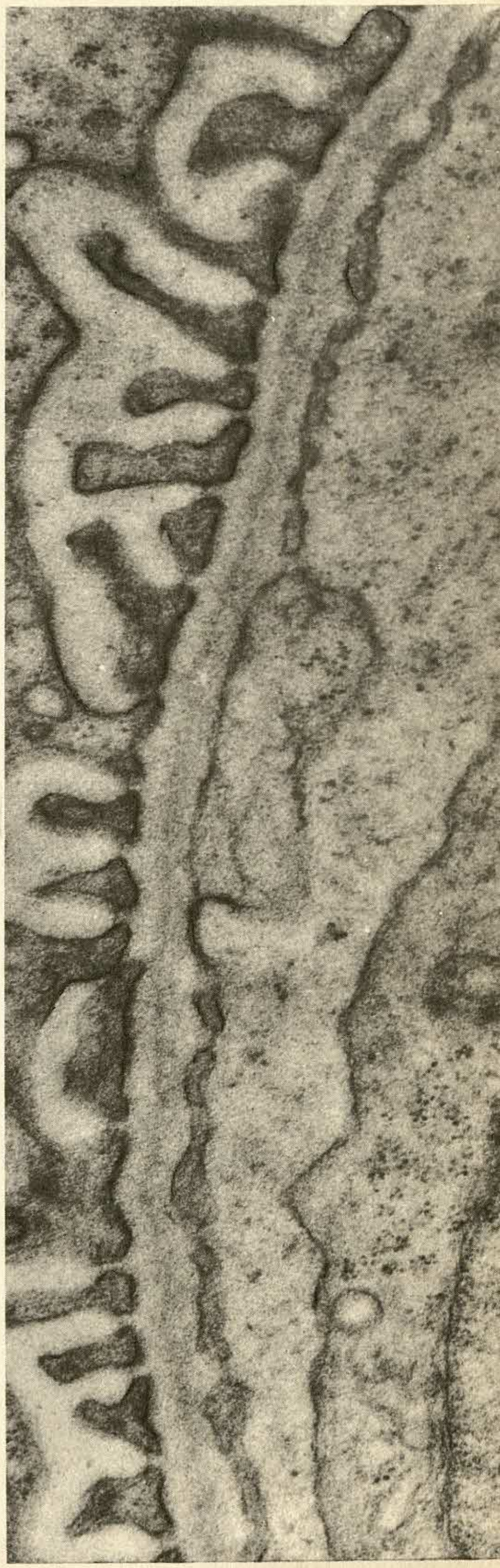
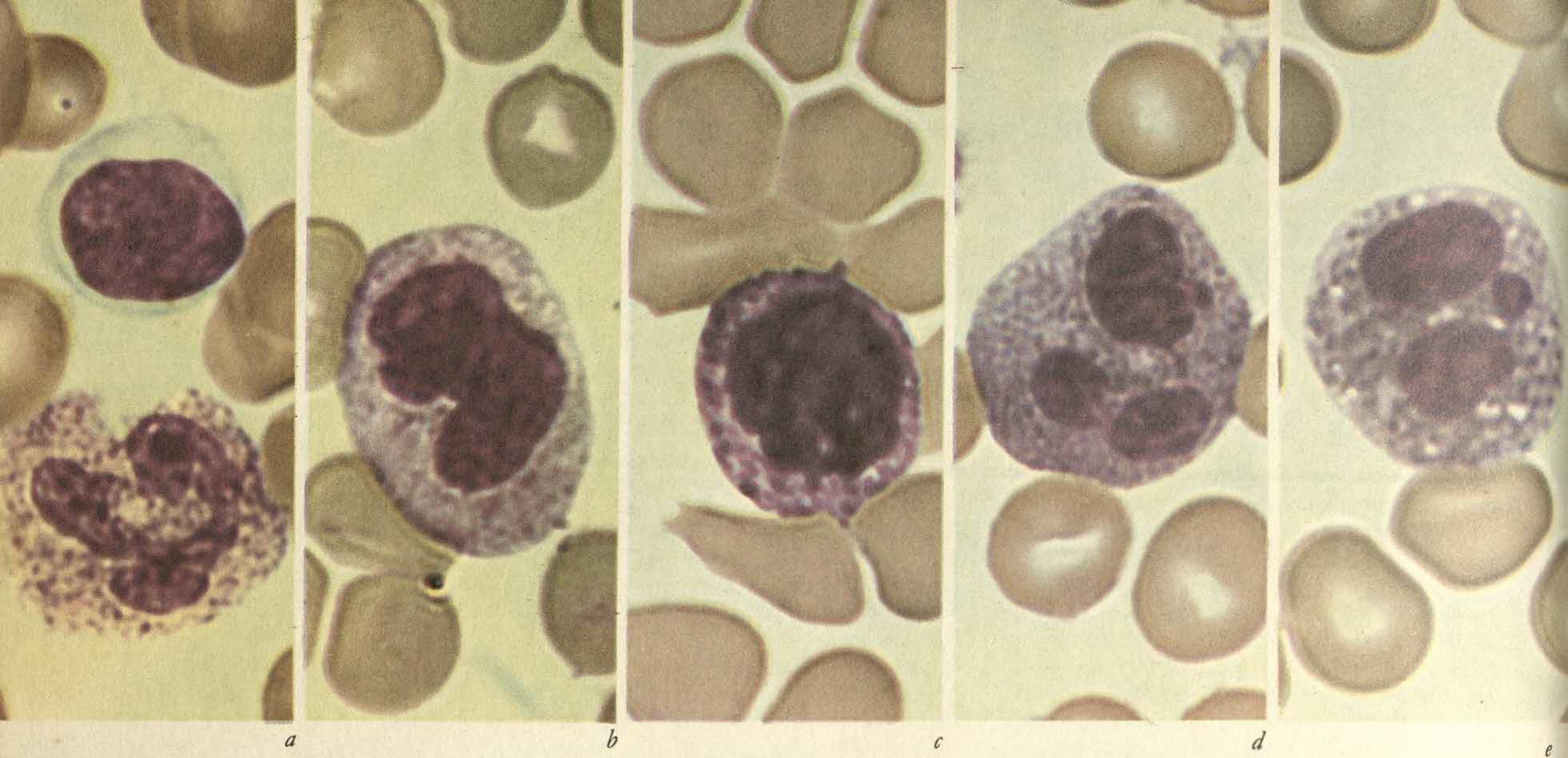
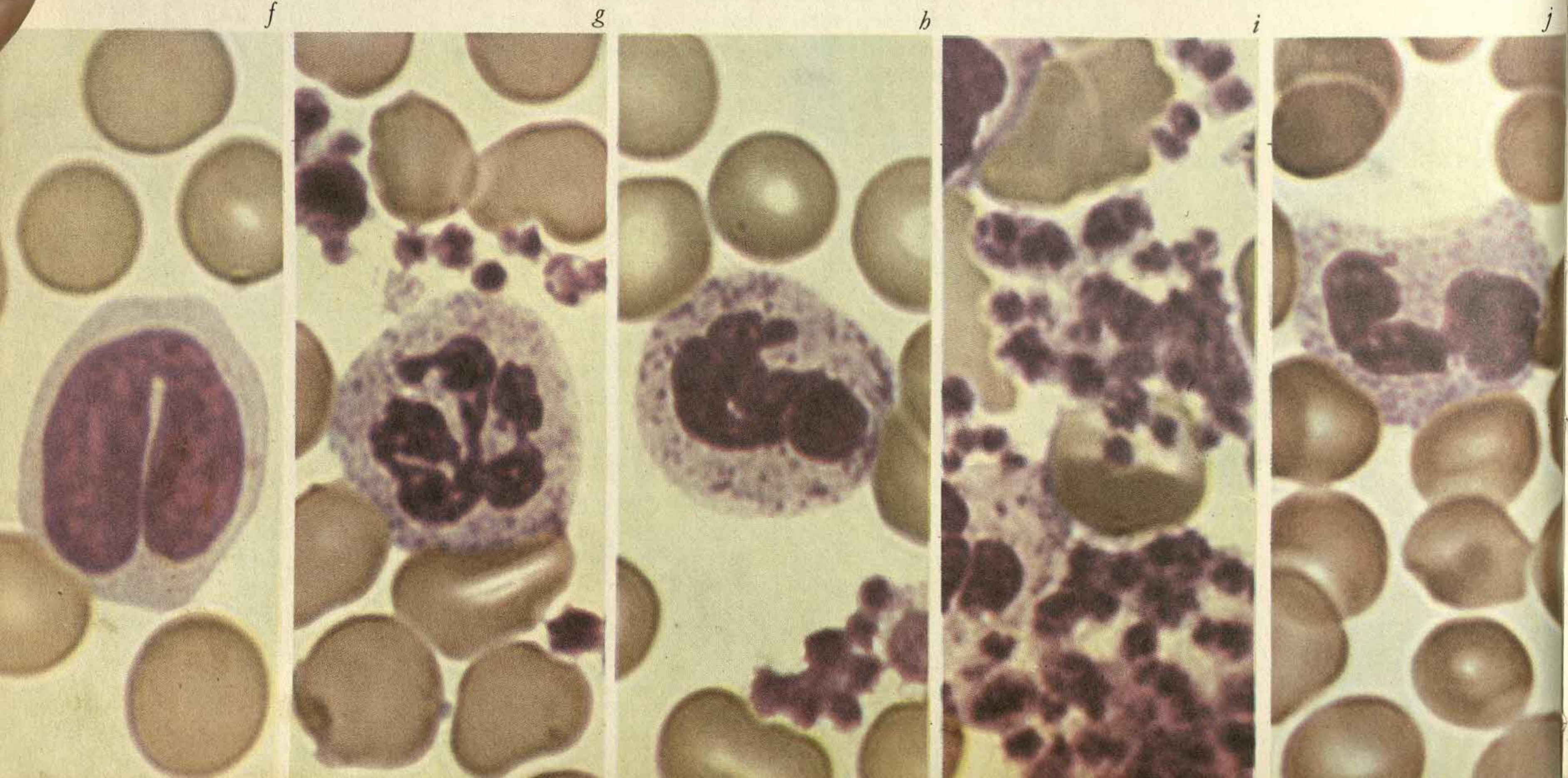


*Fig. 4. Glomerular capillary of a new-born rabbit. (Laboratory of Professor Hamburger. Mag. × 50,000).*



*The human machine could not function if it were not for the circulation of fluids known to classical authors as 'humours', the most important of which is undoubtedly the blood. In spite of its 'humoral' quality, it is nevertheless a tissue, containing cellular elements. Above and below may be seen smears which show some of these elements: (a) a polymorphonuclear cell (with a multilobed nucleus) and a lymphocyte; (b) a monocyte; (c) a polymorphonuclear basophil; (d) and (e) two eosinophil polymorphonuclears; (f) a large mononuclear; (g) and (h) polymorphonuclears and platelets; (i) monocytes, polymorphonuclears and platelets; (j) neutrophil polymorphonuclear. The background of these preparations is strewn with red corpuscles whose diameter (7 microns) makes it possible to appreciate the size of the other cells. It is well known that the quantity of blood in the organism must remain constant; that is why, in the case of considerable loss, it is necessary to transfuse blood from one individual to another, and to this end hospitals take blood from healthy individuals and store it in a 'blood bank' (facing page). (The photos of blood smears were taken in the laboratory of Professor Dreyfus, Hôpital Saint-Antoine, Paris).*



PART TWO

# Body fluids

# Blood cells

*Marcel BESSIS*

*Blood contains three kinds of cell in suspension: red corpuscles, white corpuscles, and platelets. The total volume of blood in a man weighing 70 kg (11 stone) is about 5 litres (9 pints); there are, per cubic millimetre, about 5 million red corpuscles (that is, 25 billions in all), 6,000 white corpuscles (30,000 millions in all) and 300,000 platelets (1·5 billions in all).*

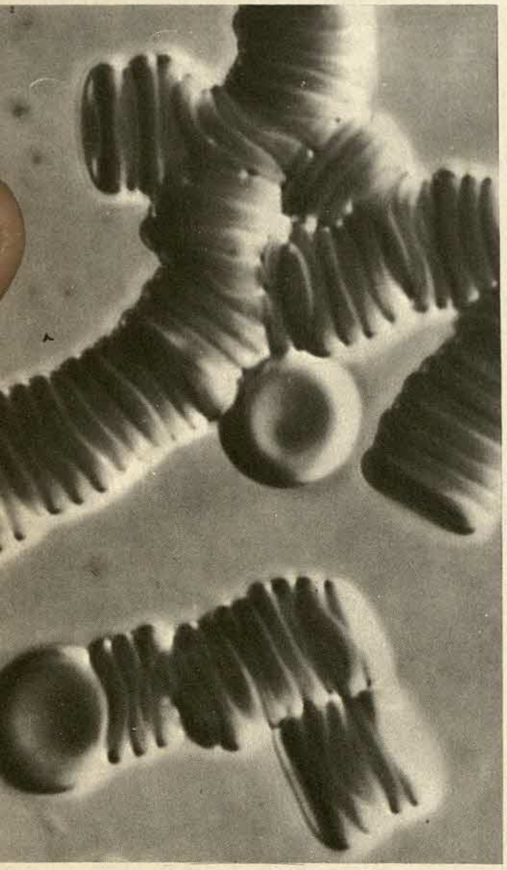


*Fig. 1. Red corpuscles seen under an optical microscope (Nomarski's interference method). The formation of rouleaux can clearly be seen. (Photo Bessis).*

The blood cells, that is, the red corpuscles, white corpuscles, and platelets, are formed in the so-called haematopoietic organs. The haematopoietic organs continually pour a fixed number of cells into the circulation, replacing exactly the corpuscles lost by ageing or destruction. Every day, a normal individual brings into circulation 250,000 million red corpuscles (10 ml approximately) and 15,000 million white corpuscles (8 ml approximately).

The volume of red corpuscles and the volume of white corpuscles poured into the circulation each day are therefore similar, in contrast to the proportion of these cells in the blood. This apparent contradiction is partly accounted for by the different life spans, namely about two days for the white corpuscles and 120 days for the red corpuscles. The number of platelets entering the circulation is 500,000 millions per day.

Assuming that the passage of the mature cells into the circulation is a regular process, it may be seen that 2·5 million red corpuscles, 120,000 white corpuscles and 5 million platelets are poured into the circulation per second.

The blood cells of adult mammals are formed in the bone marrow, the lymphatic glands and the spleen.

Certain connective cells possess, among other remarkable properties, that of production of white corpuscles. These cells, formerly called the reticulo-endothelial system, are now simply known as reticulum cells. Cradle of the blood cells, the reticulum cells are also their grave, for they destroy and remove damaged or aged cells.

## *The red corpuscles*

The red corpuscles of adult mammals have no nucleus. In man they appear microscopically as small biconcave discs, about 7·5 microns in diameter, and about 2·5 microns thick. Their colour is a pale orange-yellow. They have no movement of their own, but a fine characteristic shimmering may be visible, especially at the centre of the cell. In the blood vessels the red corpuscles are arranged in rouleaux or 'piles of coins', according to the time-honoured expression. The red corpuscles are very elastic; they are capable of elongation, so as to pass through capillaries whose diameter is smaller than their own, and their initial shape is recovered as soon as they are floating freely again.

The size of the red corpuscles varies according to the species: only 4 microns in the goat, 9 microns in the elephant. The Amphibia (frogs and newts, *Proteus*) have the largest red corpuscles. In *Proteus* they measure 55 microns and can be distinguished with a simple magnifying glass.

The red corpuscle consists of an envelope enclosing a spongy stroma whose meshes hold the pigment haemoglobin, which gives it its colour. When a red corpuscle is damaged, the pigment it contains diffuses out of the cell: this process is called haemolysis. Haemolysis may be due to hypotonic environment (osmotic haemolysis), to physical damage (freezing, mechanical injury), or to chemical action (saponin, bile salts, fatty acids, lecithin, etc, and especially by biological haemolysins). The stroma left after haemolysis appears under the electron microscope as an empty, crumpled envelope. Haemolysis has given rise to much work of great practical importance, for it is one of the most sensitive tests for reactions of immunity (complement-deviation reaction, etc).

Haemoglobin is found as an extremely concentrated solution (about 33 per cent) inside the red corpuscle; so concentrated that it is virtually saturated. Haemoglobin is a chromoprotein formed from a protein (globin) moiety to which are attached, as so-called prosthetic groups, four molecules of haem. These have characteristic absorption bands and give the compound its colour.

Haem results from the combination of a type III protoporphyrin with an atom of ferrous iron. This iron atom is bound to the four pyrrol nitrogens of the porphyrin ring, and its two remaining covalences are employed in bonding, one to a globin nitrogen and the other to oxygen. This reversible bonding is the basis of one of the main functions of the red cells, which is the transport of oxygen from the pulmonary capillaries to the capillary networks of all the organs. This transfer permits the oxidations necessary for metabolism. The oxygen which has been liberated by the haemoglobin is replaced in the blood by carbon dioxide, a waste product of metabolism. This exchange takes place very rapidly. The cardiac output in man at rest is 5 litres of blood per minute; and it may reach 8 litres or more during muscular effort, for the oxygen requirement of the organism is considerable. For example, a man weighing 70 kg (11 stone), who burns up about 3,000 calories by the combustion of food in twenty-four hours, uses about 600 litres of oxygen.

The haemoglobins differ from one another in the structure of their protein part. From one species of animal to another the amino acid composition is very variable. The normal adult haemoglobin is not the only one which can be found in man; a foetal haemoglobin, an adult haemoglobin, and at least eight abnormal haemoglobins are now known. Adult haemoglobin itself is heterogeneous.

The best-known and most important abnormal haemoglobin is that present in the blood of patients suffering from sickle-cell anaemia, an hereditary disease.

## *The white corpuscles*

Living white corpuscles appear microscopically as small gelatinous blobs, 12 to 20 microns in diameter. They are divided into several varieties: the granulocytes, the lymphocytes, and the monocytes. The most striking property of white corpuscles is their mobility. Their movements become more rapid as the temperature approaches 40° C. They change their shape, by throwing out processes called pseudopodia, which elongate and draw the main cellular mass along with them; then another pseudopodium appears, which in its turn drags along the whole cell, and so on. The white corpuscles are thus capable of creeping. They cover about 20 microns per minute; that is, about 1 mm per hour.

In their creeping movements the leucocytes are attracted by certain substances, which include oxygen, microbial toxins, foreign or injured cells. They travel throughout the body, penetrating the tissues, and can easily leave the circulating blood and return to it.

When by accident a germ or a foreign body, such as a splinter, gets into the organism, the white corpuscles immediately leave the vessels and gather at the affected part. There they actively effect phagocytosis of the germs, or attack in mass the foreign body which they try to break up or dismember. Pus is formed by their accumulation; it is composed of white corpuscles which have digested the microbes invading the organism.

The white corpuscles also play a large part in the elaboration of antibodies.

## *The blood platelets*

The platelets are the smallest elements found in the blood. They are small discs, only 2 to 3 microns in diameter, composed of cytoplasm and showing about 10 granules in their centre.

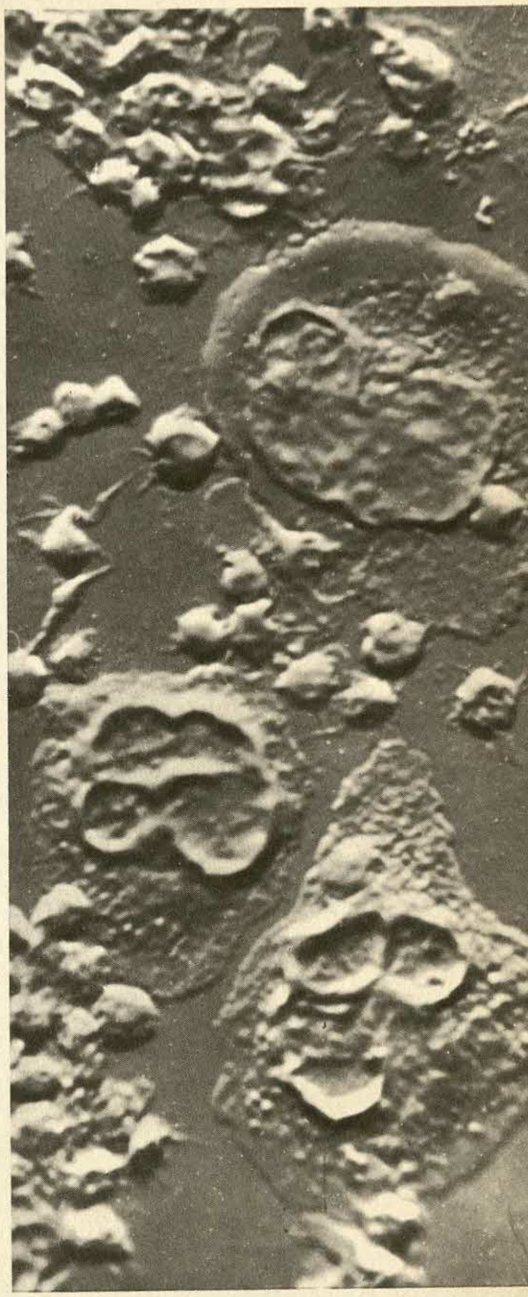
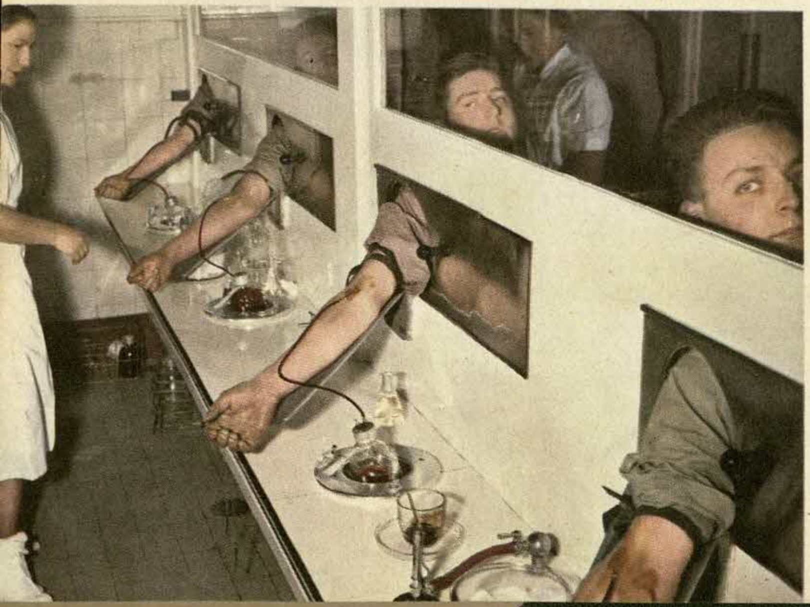


*Fig. 2. Leucocytes and platelets seen after shadowing with gold: at the top, a monocyte; at the bottom, two polymorphonuclear granulocytes. The background of the preparation is strewn with blood platelets. (Mag. × 2,000. Photo Bessis).*

*Preliminary determination of a blood group on a slide. The donor's blood is mixed with four different types of sera containing agglutinins, to avoid accidents arising from the presence in the same blood of agglutinogen and the corresponding agglutinin.*

*Waiting-room outside the collection cubicle. The donors are quite relaxed. The collection cubicle is sterile, every condition of asepsis being rigorously observed. The blood will be treated and conserved by refrigeration and desiccation.*

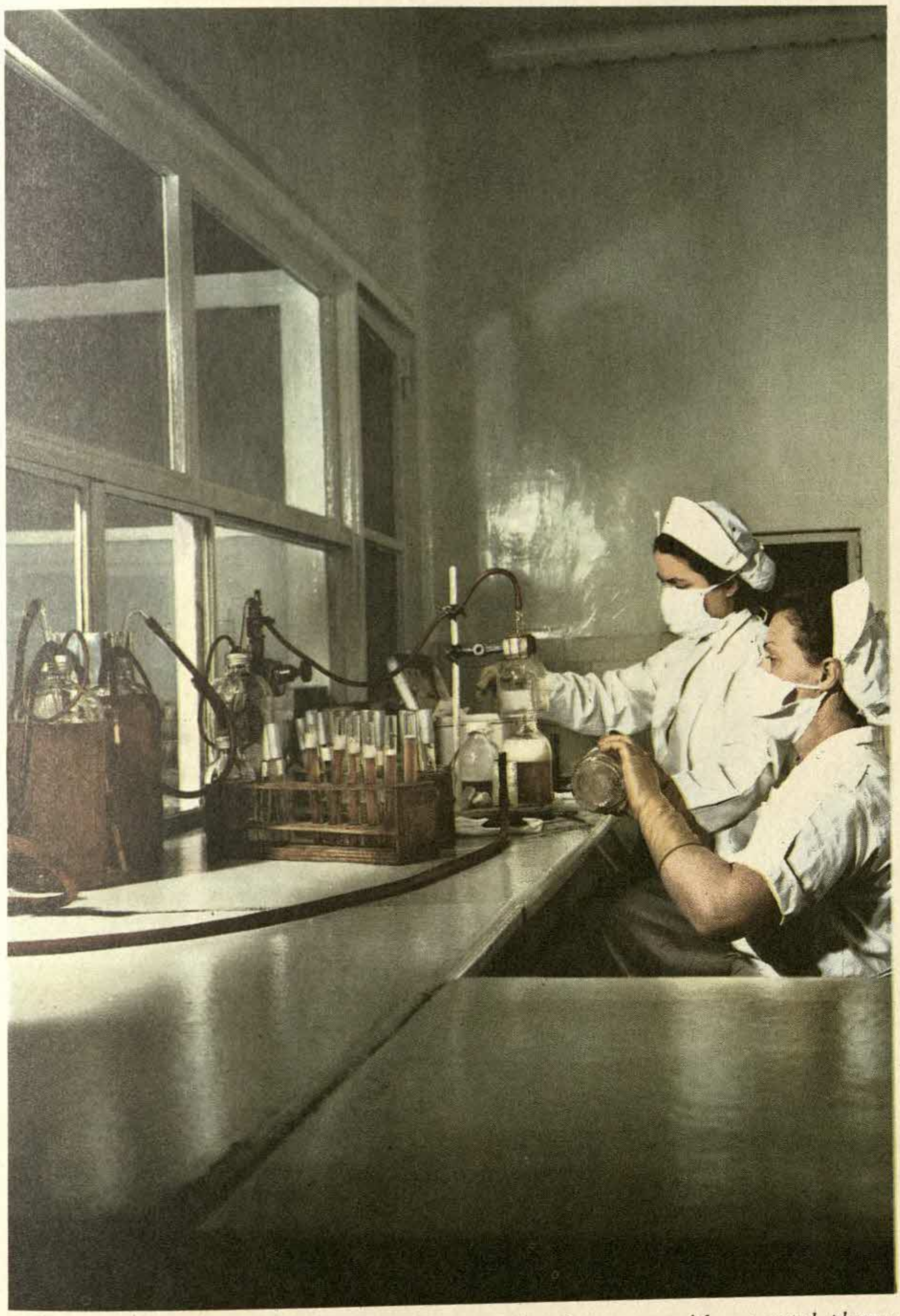


*Human blood is the most precious of all liquids: the organism must contain a constant quantity of it, and in case of considerable haemorrhage or serious illness the only way to avoid death is by transfusions. It is possible not only to transfuse blood directly from one person to another, but to collect it and then store it after the separation and desiccation of its various components. These photographs, from the Jean-Julliard military blood transfusion and accident centre, show the different stages in the collection and fractionation of human blood. The illustrations show the apparatus required for the lyophilization of blood, ie, its desiccation under vacuum from the frozen state, and also its conservation. (Photos Lod).*

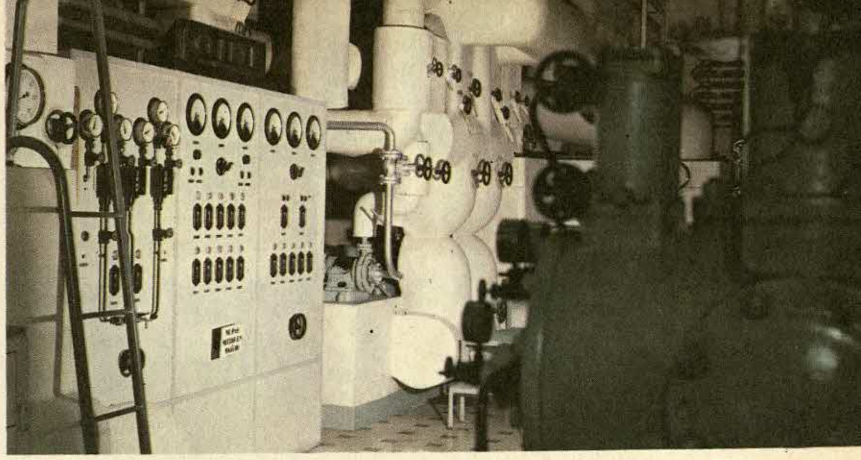
*This is what a 'blood bank' looks like. The labelled flasks, with their sample tubes, are classified by groups (A, B, O) and according to their Rhesus factor. They are kept in a refrigerator with rotating trays. Because the storage time must not be more than three to four weeks, the date of collection is also important.*

# *Collection and conservation of blood*

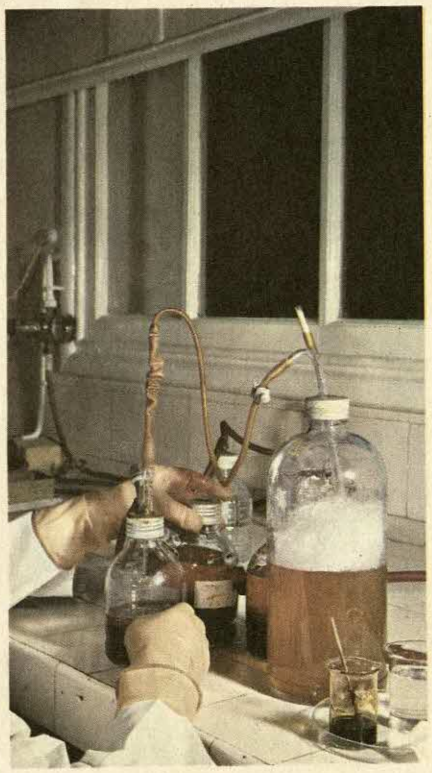
*Below is the plasma laboratory. Fractionation takes place in a sterile cubicle. Sedimentation, or better still, centrifugation, allows the plasma to be separated from the blood. It appears as an amber-yellow liquid, and consists of water, with a coagulable substance (fibrinogen) and globulins in solution.*

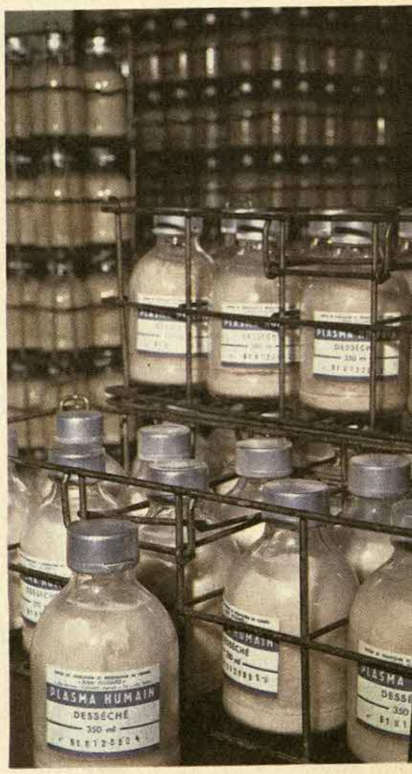


*Right is the reserve of dried plasma, either whole plasma, or with separated plasma proteins. Lyophilization ensures storage for several years without deterioration, so that whole-plasma powder reconstituted with water retains all its original properties. It is thus possible to use plasma or its derivatives up to 5-7 years after the collection of the blood.*

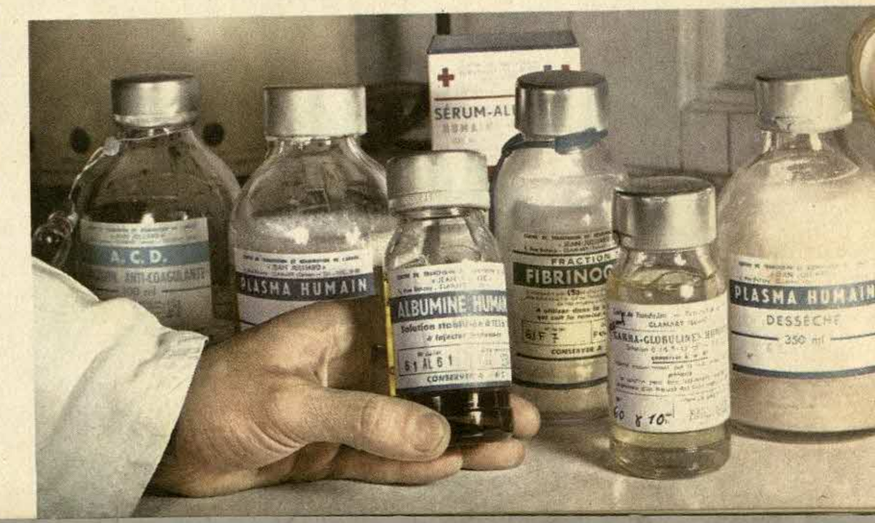


*The motor of the enormous refrigerator in the 'blood bank' shown here emphasizes the great importance of cold in this series of delicate chemical operations.*





*The pipetting of plasma: the leucocytes (white corpuscles) with their nuclei, the red corpuscles which have lost their nuclei in the course of their maturation, and the blood platelets composed of fragments of cytoplasm, are deposited at the bottom of the bottle. It is possible to separate these components and, as in the case of plasma proteins, to fractionate them for therapeutic purposes. Conservation time: 3-4 weeks. The plasma itself is transferred to another vessel by suction and passed on for desiccation.*



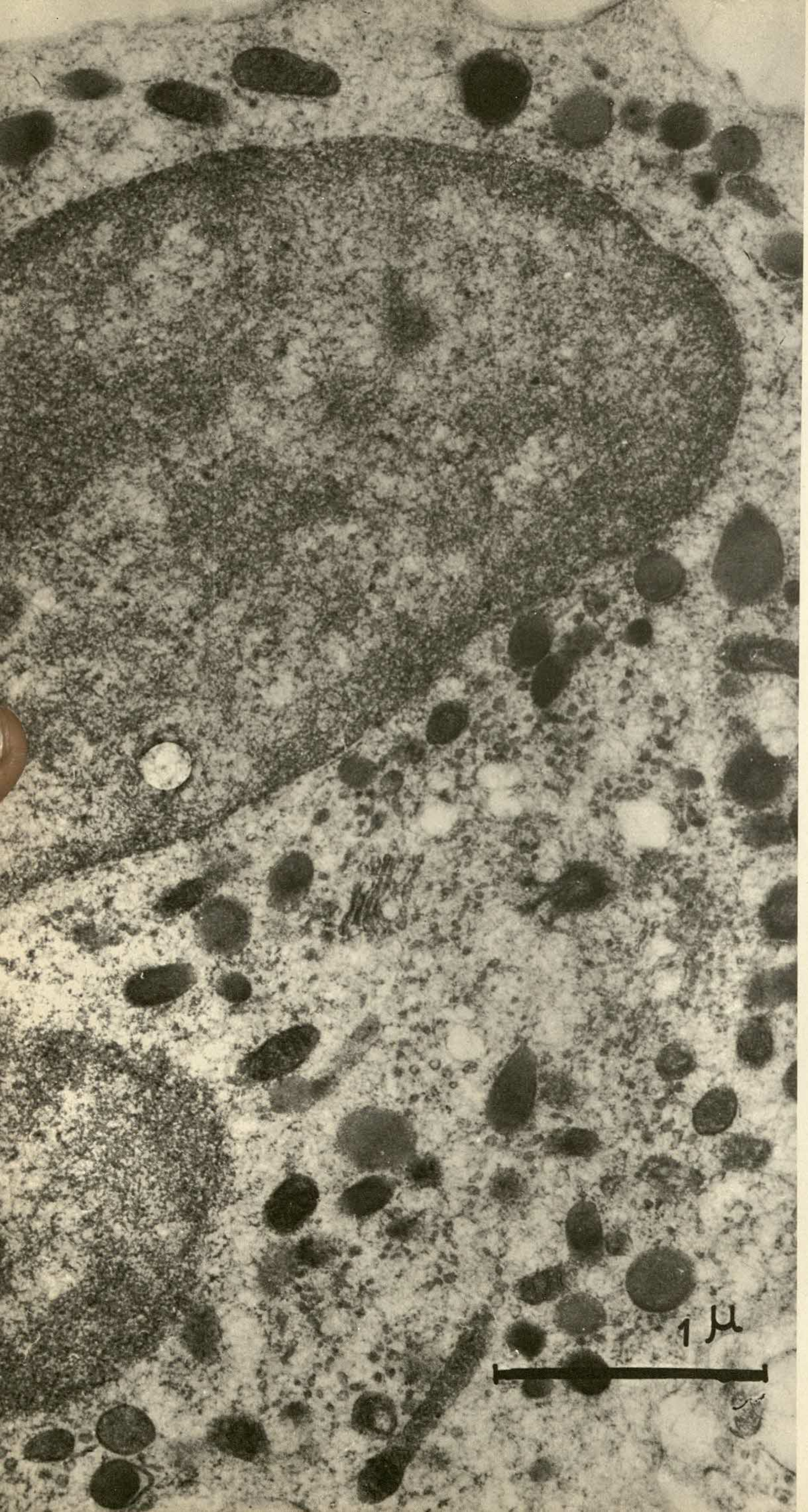


*Fig. 3. Section of a neutrophil granulocyte seen under an electron microscope. The nucleus, the neutrophil granules and the mitochondria can be recognized. The centriole has three 'satellites'. (Mag. × 35,000. Photo Bessis).*

If a drop of blood is taken and immediately examined under a microscope, between slide and cover slip, it reacts in the following way: the red corpuscles arrange themselves in rouleaux resembling piles of coins, while the white corpuscles start creeping in all directions. The platelets in their turn are seen to clump and to arrange themselves in small groups; a large proportion disintegrates spontaneously. A few minutes later refractile needles appear here and there and soon surround each group of platelets. These are needles of fibrin: their appearance marks the beginning of the clotting of the blood.

The clumping and disintegration of the platelets takes place as soon as they come into contact with a foreign surface. When blood is collected in a glass, metal, or rubber container, the platelets clump and disintegrate immediately. There are, however, ways of keeping the platelets in their normal state outside the body, at least for some time; it is necessary only to collect the blood in a container whose inner surface cannot become damp. Vessels made of plastics are excellent for this purpose.

Another means of preventing the clumping and disintegration of the platelets is to hinder the clotting of blood, using such substances as sodium citrate or heparin. If a drop of blood, to which a small quantity of these substances has been added, is examined under the microscope, the platelets are seen to remain separate. A very peculiar phenomenon of great physiological importance is then observed: the platelets throw out threadlike growths, so that they look like starfish; a few minutes later, these growths cling to the glass of the slide on which the examination is made, and spread out to form a very thin and extensive sheet. A platelet about 3 microns in diameter and 1 micron thick will adhere to the glass, and spread out to a flat disc 10 microns in diameter, but only about 0·2 micron thick.

When the wall of a small blood vessel is injured, the platelets not only stick to each other but also to the edges of the wound and spread over them, thus forming the so-called haemostatic plug. Disintegration of the platelets heralds the appearance of fibrin and, therefore, the clotting of the blood.

# Coagulation

## *Jean-Pierre SOULIER*

*Any wound or contusion could easily lead to death or serious illness if the blood did not possess the ability to clot, and thus fill breaches in the walls of the vessels. The formation of a blood clot depends on a complex mechanism which hinges essentially on the transformation of a substance, fibrinogen, normally in solution, into an insoluble form, fibrin. This transformation takes place under the influence of thrombin, which is formed from many factors, including prothrombin, calcium, and the blood platelets.*

In coagulation blood gels to a compact clot owing to the transformation of soluble fibrinogen into insoluble fibrin. The latter forms a network, retaining the red corpuscles in its very fine mesh. The clot, once formed, retracts during the succeeding hours, and allows the serum to exude. In certain pathological conditions the clot may redissolve. This is known as fibrinolysis.

The first really scientific concept of coagulation goes back to Alexander Smith (1895) and Morawitz (1905). Prothrombin, which belongs to the group of plasma proteins known as the globulins, exists in the plasma in an inactive form; it is converted into thrombin through the action of thromboplastin and calcium ions. The thrombin formed in this way is a highly active agent which is capable of transforming fibrinogen[1] into fibrin in a few seconds. This basic scheme is still valid today, but it has undergone considerable elaboration, since it has become apparent that neither prothrombin nor thromboplastin are simple proteins, as was originally believed. It is now known that, as well as the true prothrombin, various accelerators or activators are necessary for coagulation to take place (fig. 1, Table 2).

The coagulation of blood plasma in a glass tube takes place in three stages; first, the formation of the so-called intrinsic thromboplastin (formed in the absence of any tissue extract) involves two steps—an incomplete or inactive thromboplastin is formed which is then activated by the prothrombin complex; next, the active thromboplastin turns the prothrombin into thrombin; and finally, the thrombin that has been formed converts the fibrinogen into fibrin.

## *The formation of thromboplastin*

These three stages—the formation of thromboplastin, of thrombin, and then of fibrin—overlap to a certain extent.

Initially, the antihaemophilic factors of the plasma react among themselves and with a factor derived from the platelets.

The antihaemophilic factor (Factor VIII) has been known for a long time. Lack of this is responsible for classic haemophilia. It should be remembered that haemophilia is a congenital tendency to haemorrhage, most often running in families, in which haemorrhages are brought on by the smallest injuries. In particular, such haemorrhages appear as ecchymoses; haematoma or collections of blood under the skin or within the muscles; and haemarthroses, which are intra-articular

(1) Fibrinogen: *a protein present in solution in the blood, which, in clotting, is transformed into a similar but insoluble protein, fibrin.*

(2) Cohn's Fraction I: *the term used to describe a group of blood proteins obtained by a method of chemical fractionation developed by the biochemist Cohn.*

(3) Cephalin: *a lipid abundant in the nervous system.*

(4) Thermolabile: *describes an organic substance that is easily destroyed or inactivated by heat.*

(5) *In order to simplify matters, an international committee on nomenclature decided during 1958–60 to adopt Roman numerals. Until now, ten clotting factors have been described (Table 1).*

(6) *Factor VII or Factor V deficiencies* (hypoproconvertinaemia, hypoproaccelerinaemia): *an abnormal diminution in the concentration of Factors VII or V in the blood.*

(7) White thrombus: *a clot composed of fibrin and platelets, but containing few red corpuscles.*

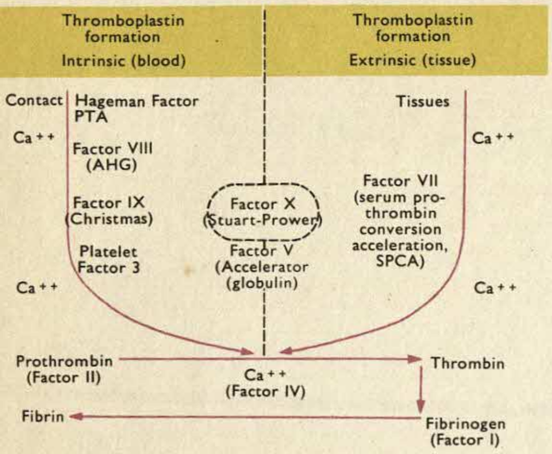


*Fig. 1. Diagram of the process of coagulation.*

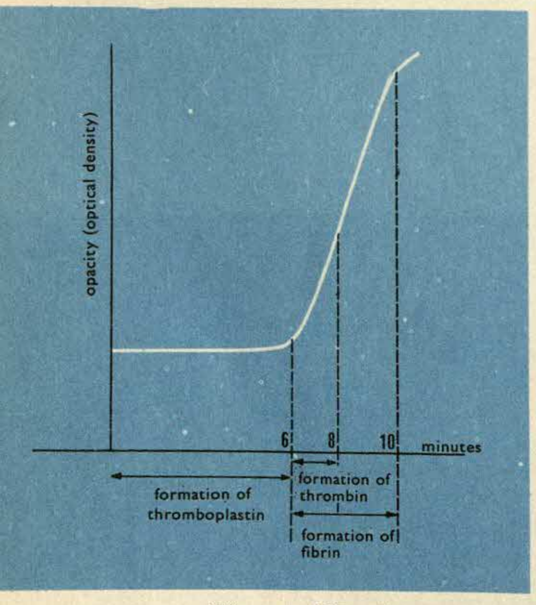


*Fig. 2. The three successive stages in coagulation: the increase in opacity of plasma treated with citrate.*

haemorrhages, possibly leading to limitation of movement and responsible for considerable disability. A cut, an accident, or a surgical operation lead to serious complications. Haemophilia is a disease affecting the male sex, but it is transmitted by females, called carriers, who pass on the haemorrhagic tendency without themselves being affected by it. Factor VIII (AHG) is present in normal plasma and is consumed (ie, disappears) during coagulation, so that it is absent from the serum. Some of its physico-chemical properties are similar to those of fibrinogen, with which it is found associated in most precipitation reactions. It is for this reason that Cohn's fraction I,[2] which contains fibrinogen, also contains Factor VIII. Further purification of Fraction I yields a potent antihaemophilic fraction that can be used in the treatment of haemophilia.

Lack of Factor IX (Christmas) is responsible for 15–20 per cent of the cases of so-called haemophilia. Clinically, Christmas disease may be indistinguishable from true haemophilia A. In Christmas disease also, a tendency to haemorrhage affecting the male sex is transmitted by female carriers. Differentiation rests on laboratory investigation. Thus it may be found that the addition of plasma from a case of known haemophilia will restore to normal the clotting time (*in vitro*) of blood from parents with Factor IX deficiency. Similarly, plasma deficiency in Factor IX will correct the defect of true haemophilia (mutal correction).

Normal blood or plasma contains the antihaemophilic Factors VIII and IX, and transfusion provides a temporary correction of the deficiency responsible for haemophilia.

An additional factor is sometimes called the activated PTA factor (plasma thromboplastin antecedent). The activation of PTA itself follows the activation of another factor, called the Hageman factor, by contact with glass or surfaces containing silica.

The platelets play an important and extremely complex part in coagulation. On contact with a foreign surface they undergo a viscous transformation and liberate their contents. Among the factors liberated, the most important for coagulation is Factor III, a lipid which takes part directly in the formation of thromboplastin. This factor appears as granules which can be centrifuged at high speed. The chemically active principle contains a phospholipid of the cephalin group.[3]

Total plasma calcium amounts to 2·5 mm (10 mg per cent); but only half of this is ionized. Calcium ions are indispensable in the activation of the profactors of the plasma.

The antihaemophilic factors and the platelets form an intermediate product which is very similar to extrinsic thromboplastin. It has long been known that the tissues contain a powerful activator of clotting. Extracts from the brain, the lung, the placenta, or even from saliva and milk, may have clotting activity. This is also true of various venoms from snakes or toads. Hence, brain extract is capable of causing blood or plasma to coagulate, not in a few minutes but in a few seconds. If, however, the brain extract is heated to 60°C, it loses a large part of its activity, because it is made up of two parts: a cephalin-like lipid part which resists heat and is a component of cephalin, and a protein part—analogous to the antihaemophilic factors—which is thermolabile.[4] Tissue extracts were quite often used before the Second World War for the treatment of haemorrhagic syndromes. Nowadays they are used only in laboratories, for a test which has been described by Quick. By 'Quick time' is meant the time taken for a patient's oxalated plasma containing an added excess of thromboplastin to clot on recalcification. It is now known that the Quick time reflects the activity of a group of factors which may be called the 'prothrombin complex'.

## *The prothrombin complex*

The first two factors contained in the prothrombin complex are Factor VII or proconvertin,[5] and the Stuart-Prower factor, or Factor X. These two were confused for a long time on account of their very similar properties.

Factor V, or proaccelerin, is a labile factor which rapidly disappears from stored plasma. The absence of any one of these factors may be the cause of a congenital haemorrhagic syndrome. There are in fact cases of Factor VII deficiency,[6] of congenital deficiencies in the Stuart-Prower factor, and of congenital deficiency of Factor V (the latter has been called by Owren, parahaemophilia). These haemorrhagic syndromes are extremely rare, and only a few dozen cases are known to exist. However, the study of such syndromes has led to the discovery of these new clotting factors, which play an essential part in the development of the different stages which culminate in the formation of thrombin.

The different factors of the prothrombin complex form, with the endogenous thromboplastin, an active thromboplastin which has been called 'prothrombinase'. This active thromboplastin is capable, in the presence of calcium ions, of converting prothrombin into thrombin.

Prothrombin is an important clotting factor because it is the raw material of thrombin. In fact, cleavage of the prothrombin molecule gives rise to the smaller molecules of thrombin. The different elements of the prothrombin complex which have just been described are formed in the liver cells. It follows that in severe afflictions of the liver a diminution in the clotting factors and a tendency to bleeding may be observed.

The drugs of the dicoumarin group are among the most important anticoagulants used in the treatment of phlebitis. They are active if taken orally, and inhibit the synthesis in the liver of the factors of the prothrombin complex (except Factor V).

## *The formation of fibrin*

The action of thrombin on fibrinogen results in the detachment of a small molecule of fibrino-peptide. The rest of the fibrinogen molecule, or fibrin monomer, condenses to polymeric chains which form the fibrin network (fig. 2).

A contraction of the clot follows coagulation. At 37°C it takes place in an hour or two. Disturbance in, or complete lack of, clot retraction is found when the plasma is deficient in platelets. Normally, the network of fibrin depends upon the platelets, which serve as foci for the contraction of the clot.

Sterilized blood, which has coagulated in a tube protected from all bacterial contamination, does not liquefy. In certain circumstances, however—before or after labour, or following surgical operations, particularly on the chest—digestion of fibrin and fibrinogen occurs and makes the blood incoagulable. This phenomenon is due to the conversion of a plasma protein called plasminogen, which is normally inactive, into active plasmin which is capable of digesting fibrinogen and fibrin.

This fibrinogen deficiency, due to an abnormal fibrinolytic activity, should not be confused with 'congenital fibrinogenopenia', which are characterized by an innate absence of fibrinogen in the plasma.

## *Inhibitors of coagulation*

In the plasma, side by side with the activators and accelerators of clotting, are found factors able to slow down or inhibit the formation of thrombin.

Some of these anticoagulants can only be used *in vitro.* They include sodium fluoride, oxalate, and citrate, which prevents the ionization of calcium. They are much used in the laboratory to stop samples of blood from clotting and they thus facilitate certain analyses (fig. 3).

Others, such as heparin, are active *in vivo* and *in vitro.* Heparin may be secreted by the organism in certain shock conditions (anaphylactic shock). This anticoagulant is often used nowadays in the treatment of vascular thrombosis of the veins (phlebitis and embolism). Its action is very complex, for it inhibits at the same time the formation of both thromboplastin and thrombin.

Haemorrhagic syndromes (known as purpura) are connected with a bleeding disease whose origin lies in the capillaries or in the platelets. The blood platelets (or thrombocytes) play an important part in the formation of the white thrombus[7] which precedes the formation of the clot of fibrin coloured by haemoglobin (red clot).

Besides purpura, defects in clotting are responsible for a large number of haemorrhagic syndromes. Laboratory tests are necessary for recognizing and classifying them.

The clotting time is much influenced by the conditions of blood-taking and of temperature and also by the method of collecting blood: a rigid technique yields consistent results. It should be noted that while defects in the clotting mechanism are sometimes associated with a prolonged clotting time, a defect in coagulation may still exist in spite of a strictly normal clotting time.

It is thus necessary to resort to more sensitive tests, such as that of determining the consumption of prothrombin during coagulation, or of measuring the elasticity of the clot formed (the thromboelastogram); or finally, to use tests which are sensitized by the addition of an anticoagulant (the test of tolerance to heparin). This completes our survey of the chief features of clotting. It has been seen that an extremely subtle mechanism intervenes, so that the blood, while not coagulating within the intact vessel, will form a clot when a vessel is damaged. In order that haemostasis (arrest of bleeding) should occur normally, not only must the clotting factors be present in normal amounts, but they must also become active at normal speeds. A highly complex chain of reactions allows the inactive profactors to be activated within a few minutes. When this mechanism is defective, haemorrhages result.

The transfusion of normal blood replaces the missing clotting factors and assists haemostasis.

TABLE I

**Nomenclature of clotting factors**

After each Roman numeral appear the principal synonyms now in use.

| | |
|---|---|
| Factor I | Fibrinogen |
| Factor II | Prothrombin |
| Factor III | Thromboplastin. Thrombokinase |
| Factor IV | Calcium |
| Factor V | Proaccelerin. Plasma Ac-globulin. Labile factor. |
| Factor VI | Accelerin. Serum Ac-globulin |
| Factor VII | Proconvertin. SPCA |
| Factor VIII | Antihaemophilic globulin (AHG). Antihaemophilic factor A globulin. Thromboplastinogen |
| Factor IX | Christmas factor. Antihaemophilic factor B. PTC |
| Factor X | Stuart-Prower |
| | Hageman factor |
| | PTA |

TABLE 2

**Formation of thrombin and fibrin**

1 Prothrombin + thromboplastin + $Ca^{++} \longrightarrow$ thrombin
2 Thrombin + fibrinogen $\longrightarrow$ fibrin

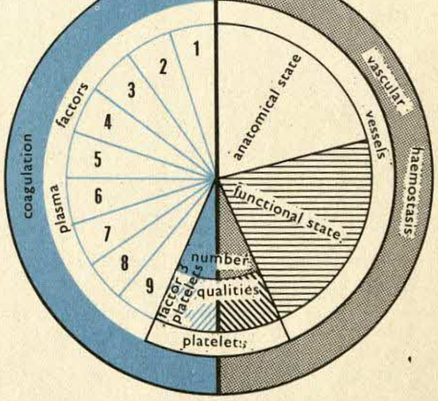


*Fig. 3. Diagram of haemostasis. Haemostasis involves the intervention of the clotting factors (blue border), vascular factors (grey border), and platelets which take part both in clotting and the vascular response on account of their properties and abundance. (1, fibrinogen; 2, prothrombin; 3, calcium ions; 4, Factor V; 5, Stuart-Prower factor; 6, Factor VIII or* AHG*; 7, Factor IX; 8, Hageman factor; 9,* PTA*).*

# Blood groups

## Paul MOUREAU

*The progress achieved in the field of blood groups during the past half-century has shown that this study must no longer be considered as a circumscribed subject, confined to the laboratory and restricted by narrow horizons. On the contrary, the pure research which has laid the foundation of this fast-expanding chapter of the biological sciences has been rapidly extended, first into medical practice, then into the public view. There is no educated person who does not know of the prodigious increase in the application of blood groups in society.*

The story opens at the beginning of the twentieth century. Landsteiner, later Nobel Prizewinner in medicine, took a decisive step forward in 1900, when he showed that in some cases the serum of one man mixed with the red corpuscles of another caused agglutination of the red cells. This phenomenon, easily visible to the naked eye, made it possible to establish that in man there are several classes of blood, which have been called O, A, B and AB.

> *'. . . owing to the blood groups we are provided with useful genetic markers not only in the sex chromosome, as by Daltonism, but in about one half of the twenty-two human autosomes also.'* FISHER

## *Groups O, A, B*

As perceptive biologists, Landsteiner and his colleague, von Decastello-Sturli, realized that the A and B properties were well-defined entities, exactly comparable to the characteristic antigens of micro-organisms already known.

This was to lead to a sensational discovery: in 1909 and 1910 von Dungern and Hirschfeld showed that the agglutinogens (agglutinable substances) of the red cells, O, A, B and AB, are transmitted according to the Mendelian laws of heredity, recently rediscovered through the work of De Vries and Correns, and Morgan and his colleagues.

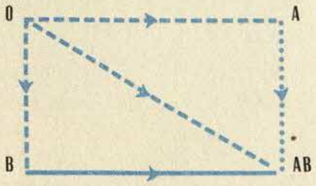


*Fig. 1. The direction of the arrows indicates the type of donor who may give blood to a recipient of another group. It is self-evident that any patient is able to receive blood from a donor of the same type as himself.*

The blood groups were soon heard of beyond the confines of the laboratory, and attracted the attention of the clinicians, for the early workers had shown that the subdivision of human blood into four groups should be used as a basis for choosing blood donors. As they had shown, the corpuscles of a given basic group may or may not possess the agglutinogens A and B, and the plasma (or serum) also may or may not contain the agglutinating substances: agglutinins anti-A and anti-B. The combinations of these two agglutinogens are shown thus:

| *Agglutinogens present in red cells* | *Agglutinins present in serum* |
|---|---|
| A | anti-B |
| B | anti-A |
| AB | neither anti-A nor anti-B |
| O<br>(A and B both absent) | both anti-A and anti-B |

This gives the characteristics of the four fundamental blood groups.

The table shows that an agglutinogen and the corresponding agglutinin cannot exist together in the same blood, for this would cause agglutination of the red corpuscles which is incompatible with life. Before the blood groups were recognized, this incompatibility was manifest when transfusions took place, for example, when A cells were injected into a person of group B whose serum is anti-A. The fundamental rules of blood compatibility were thus also determined (fig. 1).

A study of fig. 1 reveals that one type of blood is privileged as a blood donor. This is type O, which can give blood to all the other types, and which has been called the 'universal donor'. But in fact the 'universal donor' is only a myth. As early as 1911, two subdivisions had been discovered within group A and group AB: $A_1$, $A_2$ and $A_1B$, $A_2B$; while experiments on animals showed that there was such a complexity of groups within each species (the goat, for instance) that it seemed likely that human red corpuscles also displayed a variety of agglutinogens; an hypothesis later proved correct.

## *Groups M, N, P*

Between 1925 and 1940, Landsteiner and Levine discovered the factors or agglutinogens M, N and P, giving rise to groups M, N and MN, and to group P and p, thus bringing the number of known combinations to thirty-six. These factors were also inherited according to Mendel's laws, but in a manner different from the transmission of groups O, A, B and AB.

Thus the geneticists found in the blood groups one of the best illustrations of human heredity, whereas the anthropologists saw in them a means of studying the diversity or the relationship of human races, with the added advantage that their investigations could easily cover a very large number of people.

Table 1 shows the varying distribution of the blood groups amongst different peoples. There are now maps showing the distribution of the blood groups all over the world, from which some unexpected deductions about the human connections between apparently related populations can be made. Long before the Korean war, it was known that the North Koreans have the same blood-type as the Chinese, and the South Koreans the same as the Japanese. Anthropologists and geographers have interpreted this as due to contact by land to the North and by sea to the South.

## *The Rhesus factor*

Between 1920 and 1940, while research workers were doing their utmost to discover new blood groups, the number of transfusions given throughout the world had increased nearly a hundred-fold. From time to time, however, apparently inexplicable accidents occurred, although the basic laws of compatibility between the blood of donor and patient were adhered to. These accidents occurred particularly when the patient was given blood several times within a few days or a few weeks. Then, in 1939–40, Levine and Stetson, Wiener and Peters in the United States and Moureau in Liège recognized almost simultaneously the Rhesus factor, so called because it is common to the blood of man and to the blood of the monkey *Macacus rhesus*. This discovery was to revolutionize all ideas concerning the blood groups and to open the way to a new branch of science: immunohaematology.

It was known that human blood seldom contains naturally the agglutinins anti-M, anti-N or anti-P, corresponding to the agglutinogens M, N, P; and their appearance, even after repeated transfusions, is most exceptional.

The Rh factor, however, behaves quite differently. From this point of view, the white races of mankind are divided into two types: about 85 per cent of people are Rh$^+$ (positive), and 15 per cent are rh$^-$ (negative). If a rh$^-$ person receives Rh$^+$ blood he becomes immunized or vaccinated against the Rh factor. Any further transfusion of Rh$^+$ blood to a patient immunized in this way will cause him more or less serious shock, sometimes followed by anuria, jaundice, uraemia and even death.

Thus, transfusion reactions which were not understood twenty-five years ago, were accounted for. At the same time, the Rh factor was to explain a strange disease, the cause of which was variously thought to be disease of the liver, hereditary syphilis, and so on: it was haemolytic disease of the newborn. A few hours after birth, a baby suffering from this condition shows signs of acute jaundice, with extreme paleness of the skin and of the mucous membranes, and is fretful and drowsy. Examination of the blood reveals an anaemic condition, more or less deep-seated, with abnormal nucleated red corpuscles. This is due to an anti-Rh agglutinin in the mother's serum, which has filtered across the placenta during pregnancy and destroyed the Rh$^+$ red corpuscles in the foetus.

This accident is caused by an incompatibility between the blood of the mother and the child; a phenomenon conditioned by the inheritance of the Rh factor, but not itself hereditary. Let us explain this: from the genetic point of view, an Rh$^+$ person may be Rh$^+$/Rh$^+$ or Rh$^+$/rh$^-$, but an rh$^-$ person is always rh$^-$/rh$^-$. In marriages, ten possibilities may arise (Table 2 and fig. 2).

When both the mother and father are Rh$^+$/Rh$^+$, or both rh$^-$/rh$^-$, no incompatibility of the blood ever occurs between the foetus and the mother (cases 1 and 10). When the mother is Rh$^+$/Rh$^+$ or Rh$^+$/rh$^-$ and the father Rh$^+$/Rh$^+$ or Rh$^+$/rh$^-$, no incompatibility is possible, since the woman, already possessing the Rh$^+$ factor, cannot become immunized against it (cases 2, 3, 4, 5, 6).

On the other hand, when the mother is rh$^-$/rh$^-$ and the father Rh$^+$/Rh$^+$, all the children are Rh$^+$/rh$^-$ and may be affected, since their mother is capable of producing an anti-Rh agglutinin (case 7).

Finally, if the mother is rh$^-$/rh$^-$ and the father Rh$^+$/rh$^-$, only 50 per cent of the children will be Rh$^+$/rh$^-$, and thus susceptible to disease; whereas 50 per cent will be rh$^-$/rh$^-$ and thus healthy (cases 8 and 9).

It must be added that even in unfavourable marriages (mother rh$^-$, father Rh$^+$) the mother does not always acquire immunization. (It is now fairly clear that most, if not all, cases of immunization are due to bleeding

| GROUPS | O | A | B | AB |
|---|---|---|---|---|
| | % | % | % | % |
| Belgians | 46·7 | 41·9 | 8·3 | 3·1 |
| Siberians | 40·3 | 30·5 | 23·0 | 6·2 |

| GROUPS | M | N | MN |
|---|---|---|---|
| | % | % | % |
| Belgians | 28·9 | 20·8 | 50·3 |
| Indians | 60·0 | 4·9 | 35·1 |

*Table 1. It is seen that type B occurs almost three times more often in Siberia than in Western Europe; it is regarded as the characteristic Asiatic group. In the same way, type M is twice as rare in Belgium as among American Indians, who live almost entirely apart from other peoples.*

|  | *Father* | *Mother* |  |
|---|---|---|---|
| 1 | $Rh^+/Rh^+$ | $Rh^+/Rh^+$ | all the children are $Rh^+$ |
| 2 | $Rh^+/Rh^+$ | $Rh^+/rh^-$ | 50% of the children are $Rh^+/Rh^+$ |
| 3 |  |  | 50% of the children are $Rh^+/rh^-$ |
| 4 | $Rh^+/rh^-$ | $Rh^+/rh^-$ | 50% of the children are $Rh^+/rh^-$ |
|  |  |  | 25% of the children are $Rh^+/Rh^+$ |
| 6 |  |  | 25% of the children are $rh^-/rh^-$ |
| 7 | $Rh^+/Rh^-$ | $rh^-/rh^-$ | 100% of the children are $Rh^+/rh^-$ |
| 8 | $Rh^+/rh^-$ | $rh^-/rh^-$ | 50% of the children are $Rh^+/rh^-$ |
| 9 |  |  | 50% of the children are $rh^-/rh^-$ |
| 10 | $rh^-/rh^-$ | $rh^-/rh^-$ | 100% of the children are $rh^-/rh^-$ |

*Table 2. Genetic combinations of the Rhesus factor.*

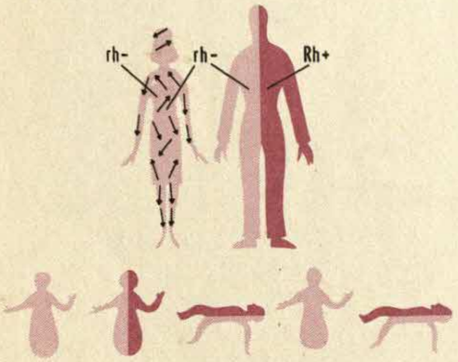


*Fig. 2. Diagram of the accidents due to the Rhesus factor in the case of the marriage of a heterozygous $Rh^+$ man ($Rh^+/rh^-$) with a homozygous $rh^-$ woman ($rh^-/rh^-$). The stippled parts represent the $rh^-$ factor; the solid red parts represent the $Rh^+$ factor; the arrows, the anti-Rh antibodies of the mother; the letter H, the healthy children; the letter S, the sick children. The first child is healthy because he is $rh^-$, like the fourth. The second child is healthy, although he is $Rh^+$, because his mother was not immunized by her $rh^-$ first-born.*

from the foetus into the mother, and a considerable proportion of them can be specifically accounted for as being due to difficult labours and obstetrical manipulations liable to damage the placenta.) Moreover, the first child is very seldom affected. There is only one exception: this is when the $rh^-$ woman has been given a transfusion of $Rh^+$ blood, even though this may have occurred when she was a young girl.

For this reason, a golden rule must be adhered to in transfusion services: in a case of emergency, when the $rh^-$ or $Rh^+$ type of a woman who has not reached the menopause, is not known, only $rh^-$ blood should be given, unless it is absolutely impossible to obtain it.

## *Five hundred thousand combinations*

The Rh factor, in fact, has been but a key to the discovery of many antigens of the type causing immunization which may give rise to transfusion reactions or haemolytic disease of the newborn. The Kell, Lutheran, Lewis, Duffy, Kidd, Graydon, Jobbins, Vel, Ven, etc, antigens may be mentioned, all of which are inherited. It has been estimated that over 500,000 combinations of agglutinogens are possible in human red cells.

We have thus reached a stage where the blood has been shown to have a real individuality: will all transfusion, then, become impossible? No; because, fortunately, many of these antigens do not bring about very active immunization, and therefore they very rarely give rise to reactions. Besides, even these can be avoided, by means of a so-called 'compatibility' test, in which a drop of the recipient's blood is mixed with a drop of the donor's red cells: the absence of agglutination shows that there is no impediment to transfusion. In the case of persons who receive many transfusions, this test should be carried out with very fine techniques capable of revealing weak immunizations. Thus whatever new danger is discovered by man in the course of his scientific research, he soon develops a means of countering it.

Furthermore, it is just those cases which cause most difficulty to the clinician that excite most interest for the geneticist. The multiplicity of group characteristics is for him a new stage in the knowledge of the patrimony of human inheritance. At the first Congress of Human Genetics, held in Copenhagen in 1956, the eminent British statistician R. A. Fisher gave expression to this in the quotation at the beginning of this chapter. By this he meant that it is hoped that links will be discovered between the blood groups and certain normal or pathological inherited characteristics. Thus a genetic prognosis would be established for individuals having a certain defect and a particular blood group. In fact, two such links have already been established, one between groups A, B, O and dysplasia of the bones and nails, and the other between the Rhesus factor and elliptocytosis (a malformation of the red corpuscles).

Another field of research which owes its success to the blood groups is that of the investigation of questions of affiliation: paternity and, in exceptional cases maternity, can be excluded, and children may be identified after exchange, kidnapping, or substitution. In 1910, the possibility of exclusion of paternity, by antigens A and B, was only 17 per cent; it is now 60 per cent or so, and it is exceptional if an unfortunate exchange of newborn babies in a maternity hospital cannot be elucidated by this modern method.

Forensic medicine, which necessarily calls upon all scientific discoveries in order the better to serve justice, has not only used the individual properties of blood to solve problems of affiliation, but has also striven to seek the blood groups in stains of blood or organic fluids (saliva, sweat, semen, etc), for the antigens resist desiccation and occur, in the case of A and B, in various secretions. This technique is indeed a tricky one and requires numerous controls, but spectacular results are sometimes achieved. A man on whom suspicion unjustly falls may prove his innocence. The identification of a very rare blood type of an accused person with that of a stain, is strong presumptive evidence in favour of the prosecution.

The biologically based discovery of the blood groups has, therefore, led to profoundly humane results: the remarkable increase of blood transfusion, the explanation of the hereditary haemolytic disease of the newborn and of other blood diseases caused by immunization, the practical application to the judicial investigation of affiliation and identification of blood stains, and finally confirmation of the validity in man of the Mendelian laws.

New horizons still lie before genetics, clinical medicine, and indeed medicine as a whole through this individuality of the blood, which may be said to provide one of the best demonstrations of the unity of biology in bringing us to a better understanding of both life and man.

# Cellular exchanges

Joseph STOLKOWSKI

*All living cells require nourishment. It is the primary condition of life: the nutrients which are needed to synthesize the material of which the cells are composed, to ensure growth and reproduction and to maintain activity, are absorbed from the surrounding medium. To accomplish these functions the nutrients are assimilated, ie, converted into living matter. This process results in the formation of waste products which would poison the cell if they were not eliminated. In this way exchanges are made between each living cell and its environment.*

In the case of the more primitive forms of life, whether single-celled or multicellular, exchanges take place between the cells and the sea water in which the first creatures lived. In man, representing the most highly evolved type of organism (as in most metazoa), the external environment is replaced by an 'internal environment', the fluid which bathes all the cells, and which, moreover, closely resembles the primitive environment.

The body fluid includes not only the blood plasma, but also the interstitial fluid (including the lymph) which is found between the vascular system and the tissue cells. It also includes the liquid within the cells themselves (intracellular fluid), the site of the first exchanges between the cytoplasm and the body fluids. Finally, there are the cerebrospinal and ocular fluids which are more localized and nourish the cells they bathe.

Fig. 1 shows diagrammatically the distribution and relative volumes of the various compartments of the body fluids in man.

The internal environment is itself in contact with the liquids and gases of the external world, either across the pulmonary epithelium or across the absorbent epithelium of the digestive tract and the wall of the excretory organs. It is clear, therefore, that our study of the exchanges between the body fluid and the cells in man is but one particular aspect of the internal environment, under the same heading as others in the physiology of higher animals: others being those of intestinal adsorption, gaseous exchanges in respiration, the functioning of the kidneys, etc, and of a more general problem affecting the very foundations of life, that of cellular exchanges.

The composition of the fluids and of the tissues, the functioning of certain organs and an analysis of the main functions, are studied in other chapters: our aim here is, therefore, to recognize the general characteristics of cellular exchanges and to seek the mechanism by which these occur.

We shall begin by noting that living cells do not have the same composition of dissolved substances (capable of being exchanged) as the medium which bathes them. The overall composition of the cellular fluids of the higher vertebrates, as measured by the osmotic pressure, is not identical with that of the internal environment; it is often higher, as in the liver and muscles, and sometimes lower, as in the red blood cells. The distribution of the dissolved substances is not the same, either: the red corpuscles and the majority of the cells in the body contain more potassium ($K^+$) than the fluids, which, by contrast, are themselves richer in sodium ($Na^+$). To take an example: in rat muscle 158 mEq of $K^+$ and 18 mEq of $Na^+$ per kg fresh weight are found, as against 4·6 for $K^+$ and 138 for $Na^+$ (in mEq/l) in the plasma.[1]

These differences disappear when the cell dies, for it then allows all the substances in the environment to diffuse indiscriminately; it may thus be said that cellular exchanges are

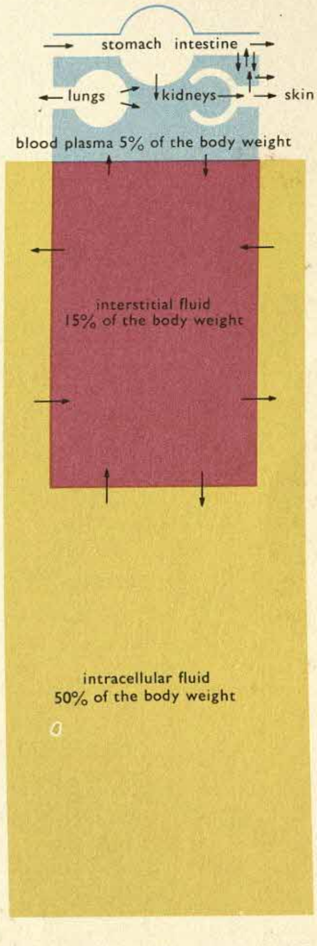

stomach
intestine
lungs
kidneys
skin
blood plasma 5% of the body weight
interstitial fluid 15% of the body weight
intracellular fluid 50% of the body weight

*Fig. 1. The compartments of the internal environment.*

not only evidence of life, but above all its primary, indispensable condition.

## *Cellular permeability*

Consider a group of identical cells in the form of a snail's heart kept alive in an appropriate physiological solution. This contains $\text{Na}^+$ 9·6; $\text{K}^+$ 9·7; $\text{Ca}^{++}$ 26·4; $\text{Mg}^{++}$ 24·8; $\text{Cl}^-$ 156·9 mEq/l. The pH is adjusted to 7·2–7·4 by means of bicarbonate. A snail's heart can survive for forty-eight hours in this medium. About two hours after removal, the organ has become 'adjusted' to the medium; it is in equilibrium with it. By this we mean that the concentration of the constituents present in the medium and in the cells ($\text{K}^+$, $\text{Na}^+$, $\text{Mg}^{++}$, $\text{Ca}^{++}$, $\text{Cl}^-$, $\text{HCO}_3^-$,) does not vary with time, contrary to what is found for a certain period at the beginning of the experiment, immediately after the removal of the heart.

It should not be concluded from this observation that exchanges no longer occur between the cells and their surroundings. If, for example, part of the $^{39}\text{KCl}$ in the physiological solution is replaced by $^{42}\text{KCl}$ ($^{42}\text{K}$ is radioactive), it will be found that this potassium passes from the medium into the cell. If, having been filled with $^{42}\text{K}$, the cell is placed in a medium without $^{42}\text{K}$ (but containing $^{39}\text{KCl}$) the radioactive potassium leaves the cytoplasm and returns to the surrounding solution. Exchanges still take place between a cell and the environment with which it is in equilibrium; however, the potassium concentration within it does not vary, because the rate of inflow is equal to the rate of outflow (fig. 2*a*).

Any relative change in this situation will give rise to a change in the potassium concentration in the cell: for example, the concentration will be increased if the inflow is raised by the addition of potassium to the physiological medium, all else remaining unchanged (fig. 2*b*); and it will be decreased if, as a consequence of some change in the metabolism, the $\text{K}^+$ ions leave the cell in greater numbers (fig. 2*c*).

This illustrates the first basic characteristic of cellular exchanges:

1. The equilibrium of the cell with its environment is a dynamic and not a static equilibrium.

If ribonuclease (an enzyme whose molecule is protedic in nature) is added to the medium, this passes into the cell. On the other hand, haemoglobin which is also a protein, cannot leave the red corpuscle, unless the corpuscle is killed, for example, by haemolysis, in which case the haemoglobin then diffuses into the medium. Cells may be permeable to certain proteins, but this is not true of all of them.

If glucose is added to the medium and the concentration of potassium in the snail hearts is determined, no change is found. The addition of cortisone to the medium, in the absence of glucose, leads to a fall in the potassium concentration. If glucose and cortisone are added simultaneously to a physiological solution in which hearts of *Helix pomatia* (the edible snail) are kept, the cells become richer in potassium. Another experiment may also be cited: if the pH of the medium is raised from 7·2 to 8, the fall in concentration produced by cortisone is no longer shown.

These experiments lead us to think that cellular exchanges are controlled by metabolic rather than physico-chemical phenomena, which are themselves, on occasion, regulated by hormones.

We can thus assume that the following two points are also characteristics of cellular permeability:

1. The permeability is selective: the living cell does not indiscriminately allow the passage of any substance; we shall see that it does not even allow those substances to which it is permeable to pass at the same speed.

2. Cellular permeability varies according to the chemical and physico-chemical composition of the environment.

In this connection, it should be remembered that the presence of metabolites in the blood after digestion is an important cause of variation in the internal environment; this variation affects in its turn the nature and intensity of the exchanges involving all the cells in the body. The normal situation is then progressively re-established by the function of the excretory organs, and by the action of certain substances which directly influence cellular exchanges. These substances include the vitamins introduced in the food itself, and the hormones released into the body fluids by the endocrine glands, which, on occasion, are acted upon by certain metabolites.

## *Seeking the mechanisms*

Since it is impossible to follow *in situ* the exchanges which take place between the cells and their fluid environment at one place or another in the body, it is evident that in seeking the mechanisms which govern cellular exchanges it is necessary to study a particular

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(1) *The notation in 'equivalents' is much used nowadays. It allows an estimate of the reactive capacity of the element under consideration, according to its concentration in solution. Account is taken of the atomic weight and the valency of the element. If C is the concentration of the element in milligrams per litre, V its valency, and A its atomic weight, the concentration in mEq/l will be given by the formula:*

$$x(mEq/l) = \frac{C \times V}{A}$$

cell or series of cells in isolation. These will previously have been placed in a physiological medium suitable to ensure survival, and of known composition.

It is difficult to remove cells or fragments of tissue in man; almost the only experiments which can be carried out are on the red or white corpuscles, or on the fluids commonly obtained from punctures of the liver, the kidney, or the bone marrow. Tissues taken from the animal or vegetable kingdoms have therefore been used for a long time. By analogy with the results obtained, if these are reproducible on different types of tissue, it can be deduced that the cells of the human body have similar properties. Red blood cells, the ova of aquatic animals, leucocytes, yeasts, bacteria, muscle cells, and axons are used for research purposes. Each category has its advantages and disadvantages. Among plants, cells and columns of cells of the Canadian water-weed (*Elodea canadensis*), of *Chara ceratophylla*, of *Valonia*, and of *Nitella* have been much used.

Isolated organs which are kept alive in appropriate physiological solutions are also used: frog and snail hearts, frog gastrocnemius muscle, pieces of the intestine of rabbit or guinea-pig, the gills of crustacea, or tissue sections from the liver, kidney, brain, etc.

Models of membranes can also be constructed, capable by analogy of giving information on the nature of the phenomena which may take place in the cellular membrane (substances which enter the cell must necessarily cross this membrane). Inert membranes can be prepared from copper ferrocyanide, collodion, or cellophane. Inanimate membranes may be used: pig's bladder, chitin taken from crustacea, vegetable membranes of pectocellulose; or living membranes, such as the skin of frogs—more complex certainly, but more easily used than the cell membrane.

Methods of study vary, but must be appropriate to the biological material. The substances whose movements are to be followed can be analyzed chemically in the medium and in the cell. Changes in the volume of the cells are studied, since these changes result from the movement of water across the membranes. Electrical measurements, particularly of conductivity, are often used. Vegetable dyes may also be useful, but it is, above all, labelled molecules which give us valuable information: radioactive isotopes, incorporated into organic or inorganic molecules which are fed to the cell, are most valuable. Acting as spies, they reveal their presence in the cell by the radioactivity they emit. 'Heavy hydrogen' is also used: deuterium $^2$H, and tritium $^3$H, incorporated into water or organic molecules, give a means of following its movements.

The development of these methods of studying the biological material available has enabled us to classify the substances to which cells are permeable.

## Gases, water, and dissolved substances

*Gases* penetrate the cytoplasm directly, in the gaseous state, or through the medium of the water in which they are dissolved. This fact is illustrated by the processes of pulmonary respiration. Of all the tissues studied, only the air bladder of fish has been shown to be impermeable to oxygen and nitrogen. The air bladder of deep-sea fishes can even store a gas containing about 80 per cent of oxygen.

The movement of gases across the membrane is due to simple diffusion, brought about by the differing pressure of the gas on each side of the cell wall. Furthermore, the more soluble the gases are in the membranes (or the lipid components of the membranes), the more easily do they pass into the cell. This property is well illustrated by the following observation: damp parchment is permeable to carbon dioxide, but not to nitrogen or oxygen, which are less soluble. Ether, which is soluble, crosses easily.

*Water:* the classical experiments of plasmolysis and the appearance of turgidity carried out on plant cells are so well known that it is unnecessary to describe them here. They show that the movement of water is determined by osmotic pressure differences between the cytoplasm and the environment. On the whole, the cell acts as an osmometer with a permeable membrane, but it must not be forgotten that colloidal gels can retain water by imbibition and lose it by desiccation; this is true of cells composed of colloids. The content in water composition of the cell depends also on the lipocytic coefficient,[2] since the fat-cholesterol mixture absorbs and retains water.

*Substances in solution:* the permeability of the cell to micelles or molecular aggregates shows itself in regard to certain organic matter, particularly to *intra vitam* stains. This penetrates the cell only when fat-soluble. Aniline blue, which is soluble only in water, does not enter. The movements of particles take place simply by diffusion; they can be followed on entering the cell as well as on leaving it.

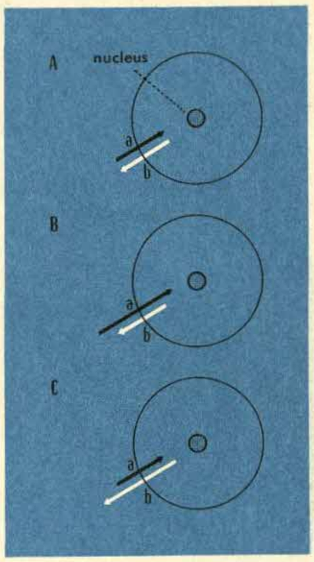
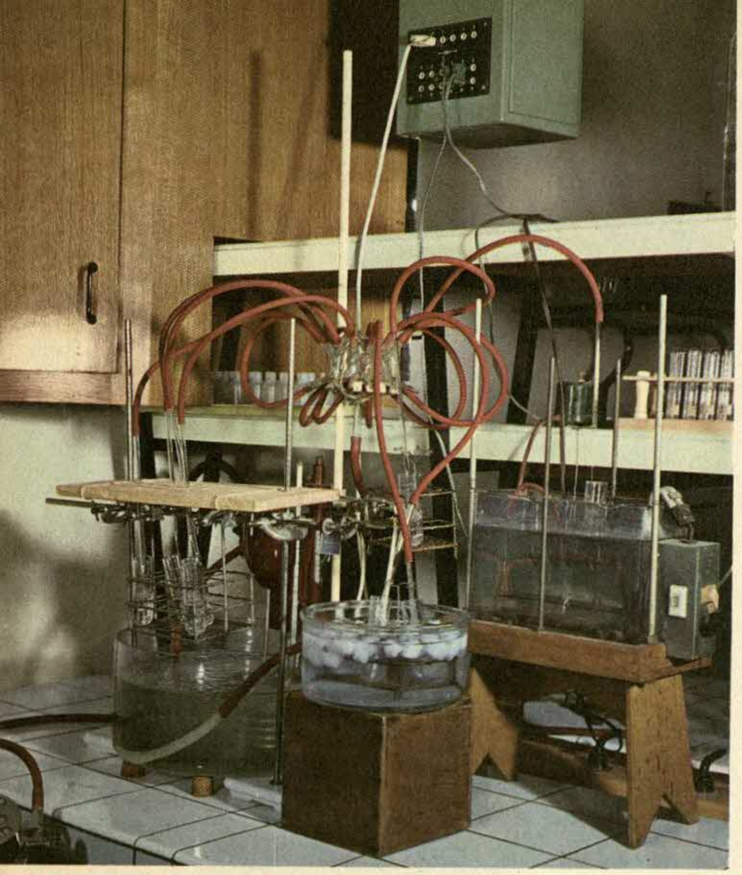


*Fig. 2. Permeability of a cell to potassium ions. (A, cell in equilibrium; B, increasing concentration of potassium ions; C, decreasing concentration of potassium ions; a, entry of ions; b, outflow of ions.)*

(2) Lipocytic coefficient: *fat content of the cell.*

# *The cellular exchanges*

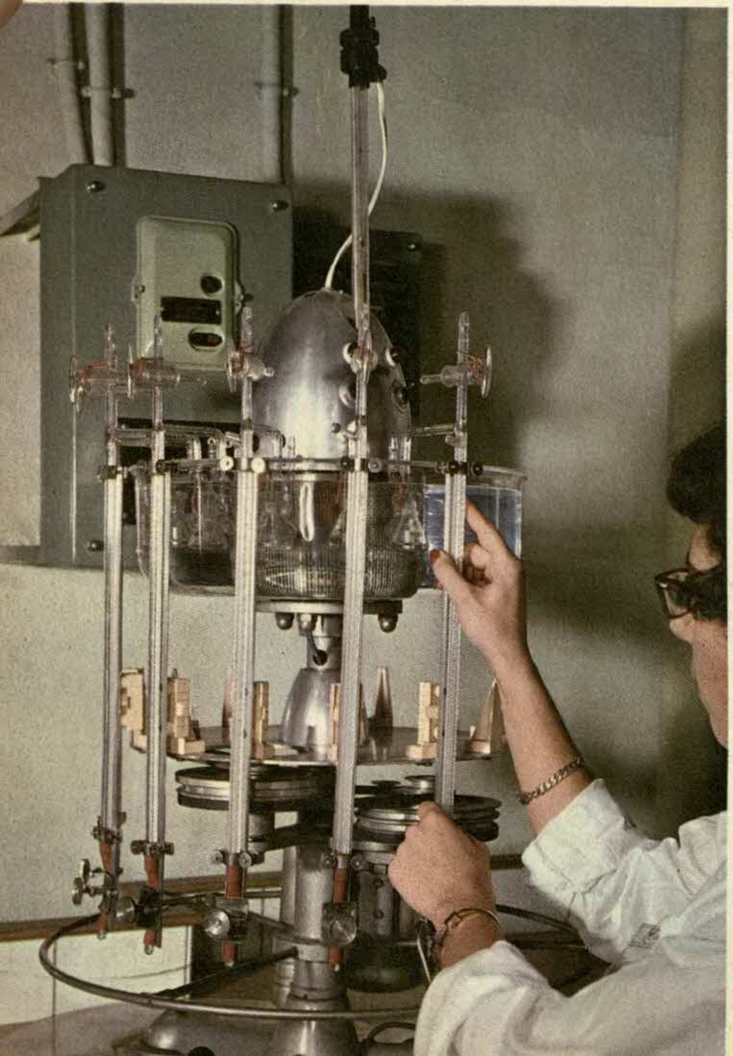
*One of the main problems encountered in discussing the human machine is that of cellular metabolism. It is now possible to measure with great precision the exchanges between the cell and the surrounding medium, with the aid of various kinds of apparatus, some of which are shown here. (Laboratory of Physiological Chemistry, Sorbonne. Photo Lod).*



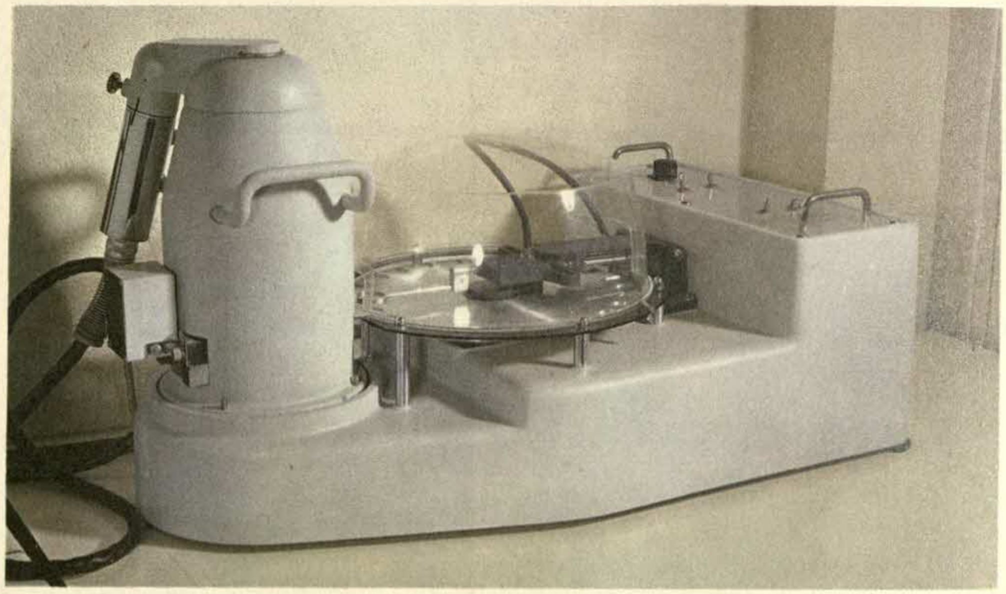
*a*

*(a) Study of cellular exchange at four different temperatures. The oxygenation is carried out by means of tubes fed from a common source.*

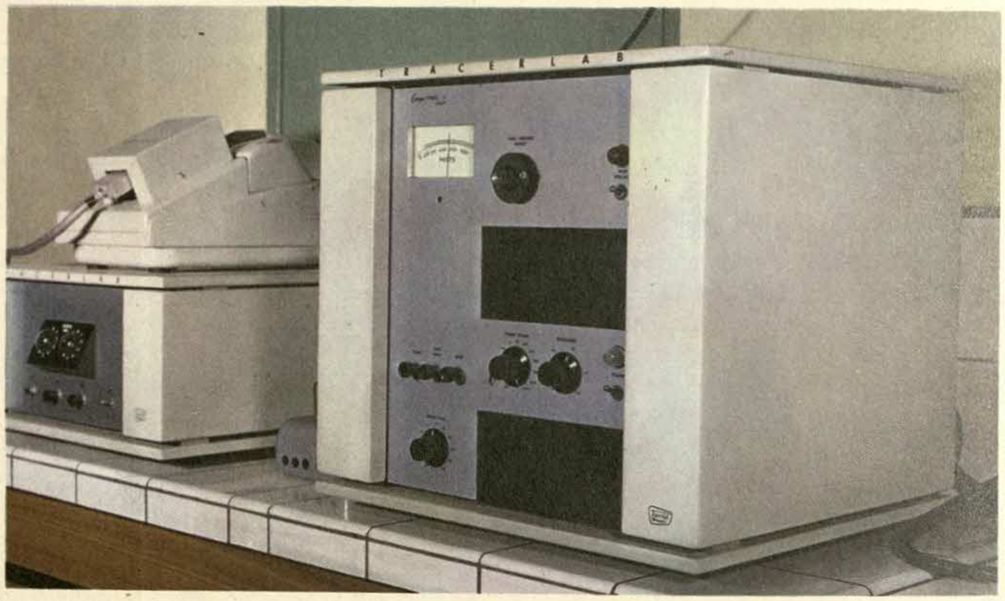
*(b) Warburg apparatus for measuring the microgas exchanges in tissue fragments. The thermostat (under the dome) maintains a constant temperature in the bath where the samples are kept. The gases are collected in capillary tubes.*



*b*



*c*



*d*

*(c) and (d) counter for measuring radio activity. (c) Right to left: automatic sample conveyor, under its dome; Geiger-Müller counter. (d) Left to right: counting instrument with high tension in the upper part; automatic recording of results. These four pieces of apparatus are arranged in series.*

*Right*
*Snail hearts kept alive in a physiological solution. The weights which keep them under tension are of unoxidizable silver and are attached by sewing thread. The heart on the left is in diastole, that in the middle in systole, and that on the right in an intermediate phase. Two hours after removal, the organ functions normally, and may survive for forty-eight hours. The extended heart is about 1 cm long. (Photo Lod).*

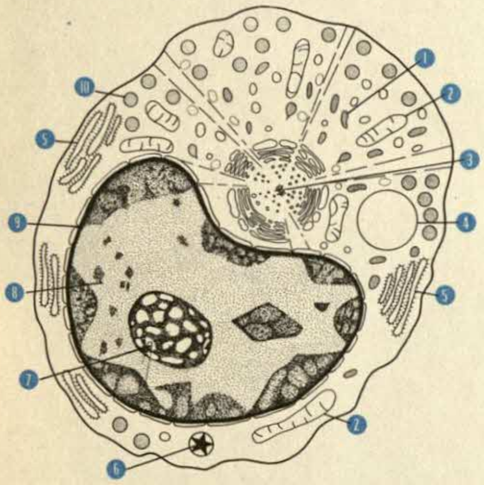


*Fig. 3. Diagrammatic representation of a cell (neutrophil myelocyte). 1, mature neutrophil granule; 2, mitochondrion; 3, centriole; 4, contractile vacuole; 5, ergastoplasm; 6, lipid vacuole; 7, nucleolus; 8, nucleus; 9, pore; 10, immature azurophil granule.*

Molecules of non-electrolytes and weak electrolytes (alcohols, aldehydes and ketones which are fat-soluble) enter the cells; glycerine is known to cross the walls of the intestine. Anaesthetics—chloroform and ether—which are fat-soluble, easily penetrate the cells. This explains the selective action of anaesthetics on the nerve centres, which are rich in lipids. The hexoses, which are soluble in water but insoluble in fats, are all absorbed at the level of the intestinal wall, but at the level of the kidney a selection is exercised: by introducing a sugar solution into the aorta at a constant pressure of 60 ml of water, Hamburger has shown that, in the frog, glucose is retained in the blood, while laevulose and mannose pass into the urine. The only difference between these compounds lies in their stereochemistry. It has also been found that the passage of glucose into the urine depends on the calcium ($Ca^{++}$) concentration of the perfusing liquid.

The red corpuscles in man are permeable to glucose (as in the monkey, but not in other species), to urea, to carbonic acid, and to water.

Generally speaking, the permeability to ions is less than to neutral molecules; furthermore, all ions do not penetrate the cells with equal facility. The most important cations in biology are: $Na^+$, $K^+$, $Ca^{++}$, $Mg^{++}$, $Li^+$, $Rb^+$ and the ion $H^+$. Amongst the anions, $Cl^-$, $Si_4^{--}$, $PO_4^{---}$, $HCO_3^-$, and $OH^-$ are notable. $K^+$ penetrates the cells more easily than $Na^+$, but $Ca^{++}$ does not easily enter. The ions can be arranged in decreasing speed of passage as follows: $Rb^+ > K^+ > Na^+ > Li^+ > Mg^{++} > Ba^{++} > Sr^{++} > Ca^{++}$ for the cations and $I^- > Br^- > NO_3^- > Cl^- > SO_4^-$ for the anions.

There is no lack of examples of ionic transport, either from the interior of the cell to the exterior, or from the exterior to the interior; thus the cells of the glands which produce the pancreatic juice release $HCO_3^-$ ions into the lumen of the pancreatic ducts and $H^+$ ions into the blood.

The red blood cells behave as though impermeable to all cations except, perhaps, $H^+$ ions; they are very permeable to the ions $Cl^-$, $HCO_3^-$, $OH^-$, but practically impermeable to the large anions, ferricyanide, citrate and tartrate.

## Variations in permeability

The properties of protoplasm are not constant: we have seen that they change with the condition of the environment, and also with the physiological state of the cell under consideration. How else, for example, could it be explained why the acinar cells of the pancreas secrete their digestive juice only during digestion?

Among the physical factors capable of affecting permeability, heat, light, ultra-violet rays, x-rays, and the radiations of radioactive materials in general increase the permeability. Trauma may also have an effect. Among chemical factors, the action of the hormones, which takes place directly at the cell level, is particularly important. Cortisone acts in this way specifically on the exchanges of potassium, whose concentration in the cell is reduced, while aldosterone acts especially on the movements of sodium. It is a curious fact that their influence on the inflow of the ion in question is not necessarily identical to their effect on the outflow; deoxycorticosterone, which inhibits the entry of $K^+$ into snail hearts kept alive in an equilibriated salt solution, has little or no effect on the outflow of this ion. The two processes are of a different nature.

The presence of certain salts in the external environment profoundly modifies the absorption or excretion of a given ion. It has been found that the monovalent cations $Na^+$ and $K^+$ increase the permeability of cells, whereas the bivalent and trivalent cations diminish it. In the case of the anions, their role varies not only with their own valency, but also with that of the cation with which they are associated.

We must also mention pH, a physico-chemical factor, the value of which depends on the concentration of $H^+$ and $OH^-$ ions in the medium ($H^+$ ions often reduce the permeability, $OH^-$ ions increase it); and osmotic pressure, an increase of which in the medium stimulates the entry of potassium into the cells.

## Passive and active transport

In seeking the mechanisms of exchange, several different problems arise. It must be explained how a substance which passes into or out of a cell can cross the cytoplasmic membrane, for this apparently forms a formidable barrier between the living and the inert media; next, it must be explained how the molecule or ion, having crossed the barrier, can reach the interior of the cytoplasm. Finally, the reasons for the selective power of the cytoplasm remain to be explained.

Various authorities have attempted to interpret the crossing of the cell membrane in terms of the intervention of physico-chemical or chemical factors: the Donnan equilibrium of the membrane, valid in certain cases; the influence of surface electrical phenomena; and the presence in the membrane of pores of variable diameter which would allow the passage only of molecules of a certain diameter. Account must be taken, in the case of an ion, of the value and nature of its electrical charge, since the interior of the pore would itself be electrically charged. Finally, we have seen that the solubility of a compound in lipids may facilitate its passage across the membrane.

The movement of ions and molecules is divided into two categories: passive transport and active transport.

Passive transport is characteristic of cellular transport which occurs under the influence of physical forces alone. This will follow, for example, from differences in the concentrations, activity coefficients, or electrical potentials between the phases which are in contact with the membrane, or from the carrying strength of a solvent when it crosses the membrane. These forces may act singly or in combination, and from their operation the diffusion of the substances considered will result; examples of this have been given.[3]

Active transport means the transfer of a substance from a medium in which its concentration is low to one where its concentration is higher, or from a medium of low electrochemical potential to a medium of higher electrochemical potential. Such a displacement, which is exactly the opposite of passive transport, implies the provision by the cell of energy for the transport system. A. Krogh (1946) was the first to use the term 'active transport'. R. B. Dean (1947) likened this mechanism to a 'pump', a term which has often been used since in a number of theories.

Active transport is especially relevant to the displacement of ions, and it is applied particularly to the movement of $K^+$ and $Na^+$. To discover why the tissues accumulate an enormous quantity of $K^+$, while $Na^+$ remains in the plasma, is one of the most important problems of contemporary physiology.

In fact, it does not seem that the movements of $K^+$ ions always result from active transport, despite appearances. It is particularly in the displacement of sodium from the interior of the cell to the exterior that the intervention of active transport has been unquestionably established.

Ions other than $Na^+$ (and perhaps $K^+$) experience active transport in the animal kingdom. Thus $Cl^-$ undergoes active transport in the gastric mucosa and in the gills of the eel. Iodine is accumulated in the thyroid. The $H^+$ ion also undergoes active transport in the gastric mucosa. Among organic substances undergoing active transport, certain amino acids and sugars are worthy of note.

One of the best-known aspects of this mode of transport is connected with the enforced exchange of $Na^+$ and $K^+$ (in the skin of amphibia, the kidneys of mammals and fishes, and the nerves of vertebrates and invertebrates) and of $Na^+$ and $H^+$ ions in the kidney of vertebrates or in frog-skin.

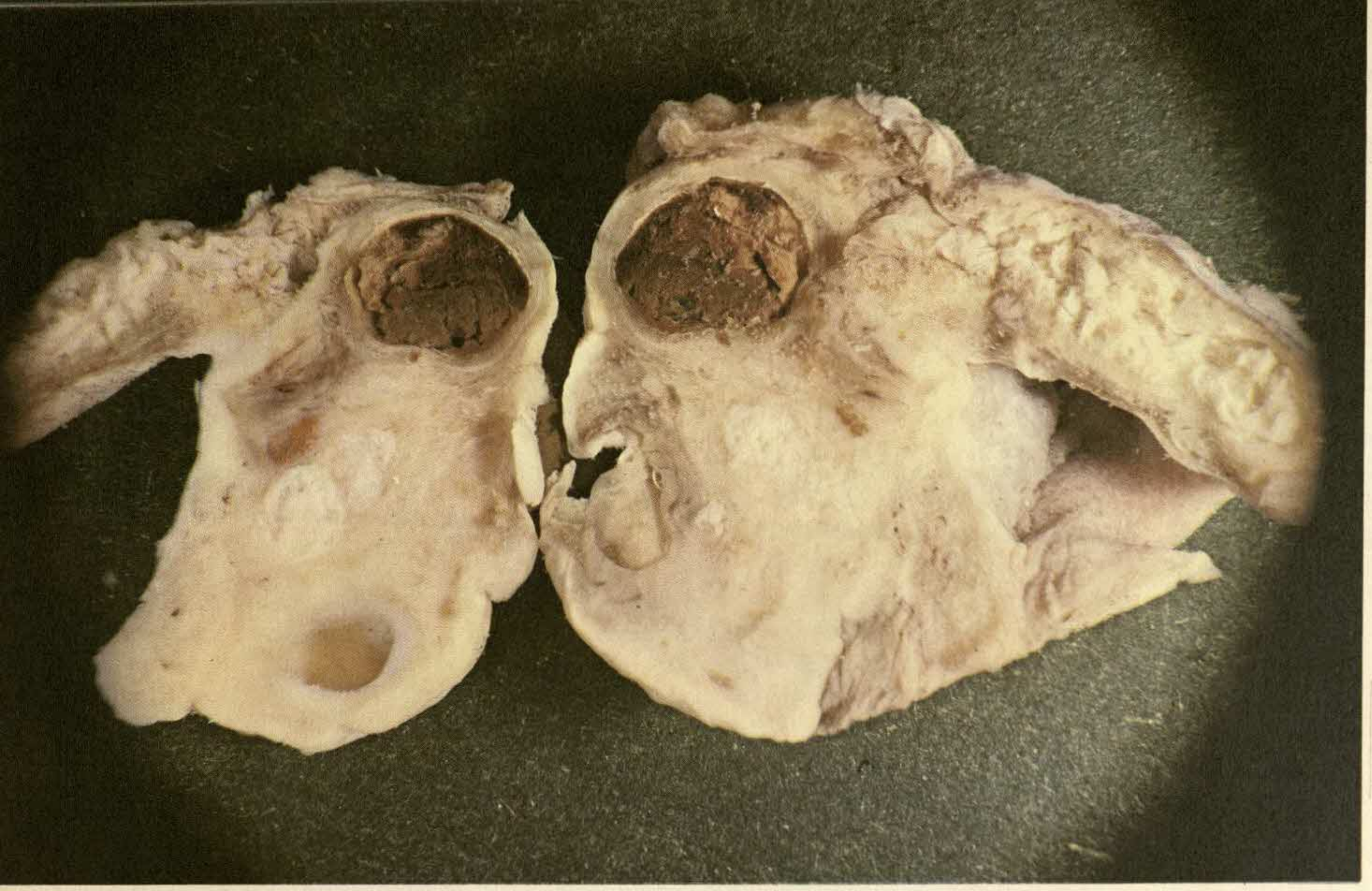
We can only resort to hypotheses to explain these phenomena and there is not space here to review very many of them. Let us mention only the ideas of H. Lundegardh (1951–1954) who explained the transport of ions, which he linked with the movement of electrons, in terms of an electrochemical phenomenon involving the transfer of electricity from one point to another; and of E. J. Conway who modified this hypothesis into the concept of the 'redox pump'. Conway has postulated the existence of a substance forming a complex, with cations, which moves along an oxido-reduction chain. Conway and his colleagues have carried out many experiments on yeast in support of these ideas.

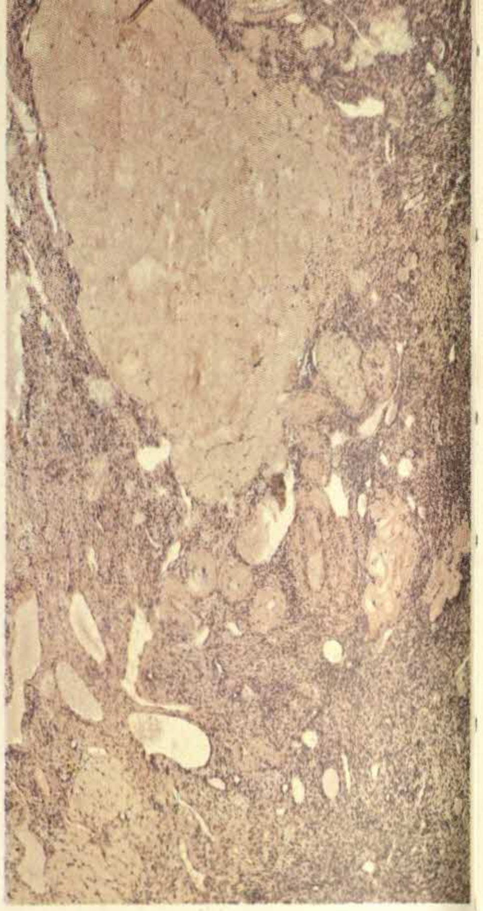
Independent of the theory of active and passive transport, the theory of G. Ling may be mentioned, in which he compares the protoplasm in its entirety with an anionic resin selectively binding cations. In this theory, the cytoplasmic proteins and anions play the essential part. It is then quite unnecessary to implicate an energy-supply in explaining the movement of the cations. This energy is needed only for the re-synthesis of the anions and proteins constantly hydrolyzed within the cell. For Ling the membrane no longer has any special activity; the ionic selectivity is a consequence of the properties of the cytoplasm as a whole, and does not depend on the possibility of a substance crossing the 'membrane' or not.

This theory is the object of heated discussion. Up till now, Ling has been the only person not to accord a specific function to the cytoplasmic membrane. It is, however, worth noting that Stolkowski and his colleagues have for several years been able to carry out various experiments in the study of certain aspects of cellular exchanges without needing to use the concept of the membrane.

It is obvious that much remains to be done before it is possible to interpret clearly the many facts which research workers have accumulated in the vital field of cellular exchanges.

(3) *In fact, the situation may be more complicated: H. H. Ussing (1947) put forward the hypothesis that ions might undergo transport in transitory combination with a 'transporter' present in the membrane and cytoplasm; its nature was not specified. According to Stolkowski and Reinberg (1958), it is possible that molecules of ribonucleic acid* (RNA) *could act as one of these transporters.* RNA, *which is constantly being synthesized and broken down in the cells, would behave as though it were a 'potassium mill', retaining the ion while in the process of synthesis and releasing it on degradation; bonding between* RNA *and* $K^+$ *has been detected by the above authors, but it must be looked at from a dynamic point of view and not as a stoichiometric combination. This hypothesis would explain the chief characteristics of the exchanges: (1) in the equilibrium state, exchange of* $K^+$ *between cell and environment would take place as a result of the constant renewal of the* RNA *in the cell; (2)* RNA, *at least in a certain chemical configuration, would specifically retain and release* $K^+$*; (3) exchanges could vary with the chemical composition of the environment, to the extent to which this would influence the synthesis of* RNA. *If the quantity of intracellular* RNA *increased, more potassium would be retained in the cell, and* vice versa.





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*The functioning of the organism is regulated largely by substances secreted by certain glands called 'glands of internal secretion'. These substances, the hormones, are varied in their chemical composition; the principal glands of internal secretion are the sex glands, the pituitary, the thyroid, the suprarenals, and the pancreas. The photographs above show ovaries and a section of ovarian tissue. The photographs below show, from left to right, sections of testis, suprarenal, thyroid and pituitary. On the page opposite is a greatly magnified picture of a pituitary. (Photographs by Lod, taken in Professor Jean Gosset's laboratory from a preparation made by Madeleine Boucher, and in the laboratory of Professor Raoul Kourilsky, Hôpital Saint-Antoine, Paris.)*

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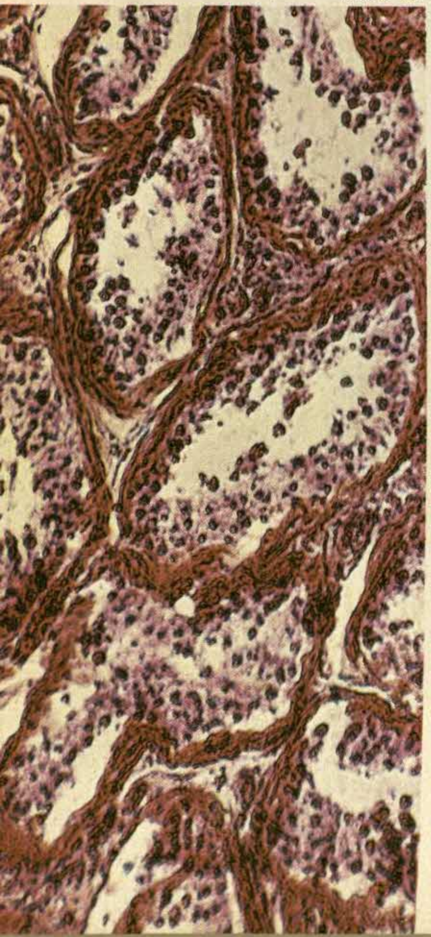

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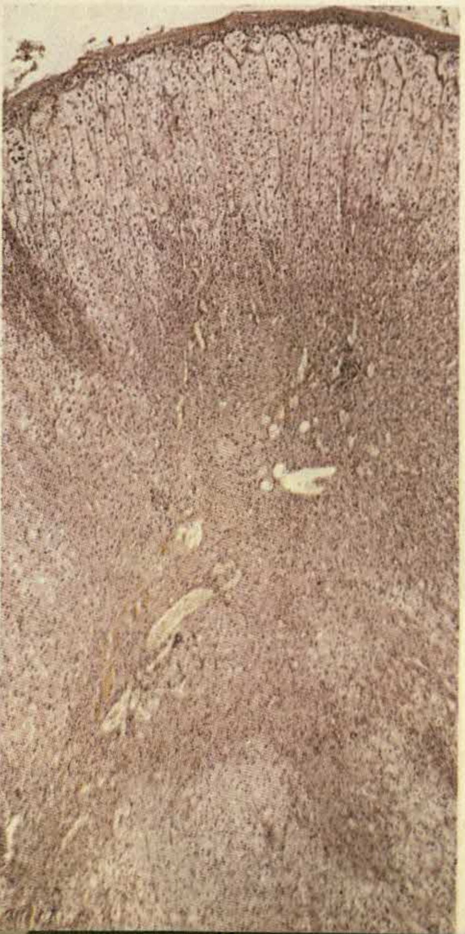

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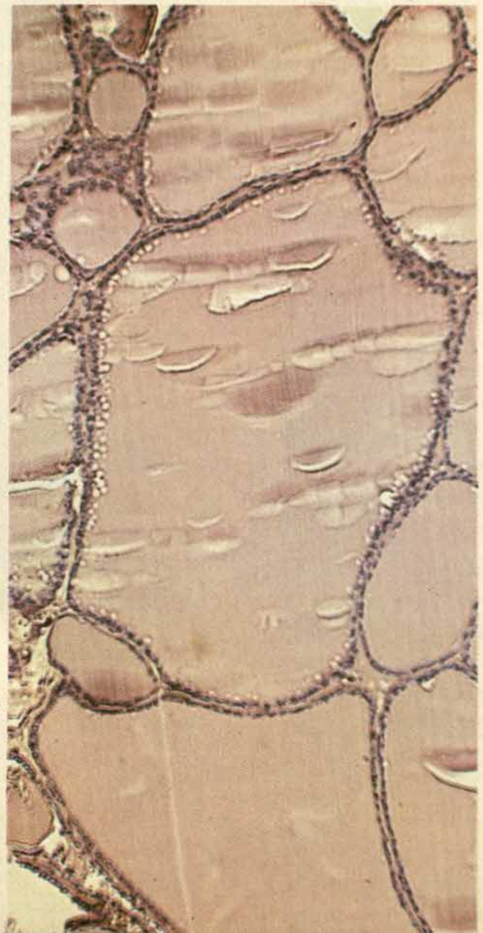

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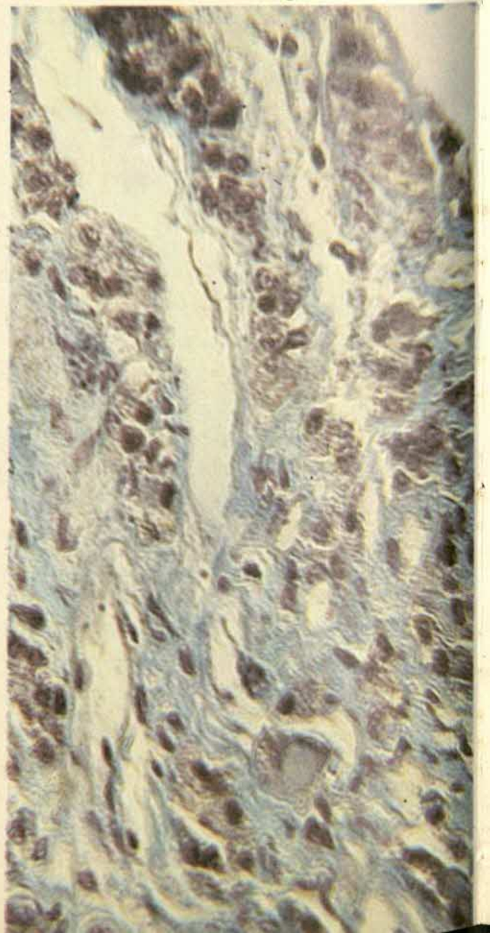


# PART THREE

# *Hormones*

# Enzymes, vitamins and hormones

*Albert DELAUNAY*

*All organic compounds result from complex combinations of four simple elements: carbon, which in the uncombined form in coal provides a fuel for heating purposes, and hydrogen, oxygen, and nitrogen, three gases without colour, smell or taste.*

However strange it may seem, organic matter is nothing but this:

'The fragrance that swells the petals of a rose, the succulent substance of fruits, the golden dust of the wings of a butterfly, or to speak like François Villon, "the body of a woman, so tender, smooth, soft and precious" . . . the poet sighs:

*There is a blue of which I die,*
*For it is in the pupils of the eye.*

The chemist replies: carbon, hydrogen, oxygen, nitrogen.'[1]

How is such a miracle achieved? What factors enable an organism to construct from so few elements all those compounds, of such diverse structure and of varied actions, that make up the human body? These factors are most certainly numerous, but the most important fall into three main groups: *enzymes, vitamins* and *hormones.*

## Enzymes

What is an enzyme? One answer would be that an enzyme is a biological catalyst governing the destruction and also the building-up of organic substances. The existence of enzymes has been known since 1833. They were discovered by Anselme Payen and Jean-François Persoz, who isolated the first enzyme (which they called diastase) and distinguished the fundamental characters of an enzyme. The great field of enzymology was later explored by Pasteur and then by Berthelot, Duclaux and thousands of others. What is known about enzymology today? A survey of the field elicits first a very natural admiration for the talent of those who were pioneers in it, followed soon afterwards by a feeling of awe at the infinite complexity of what is involved.[2]

Are there many enzymes? They are innumerable. They occur in every cell and in all parts of the cell, in both the nucleus and the protoplasm. (They are particularly plentiful in the mitochondria.) Many have already been isolated, purified and even crystallized; examples of these are urease (1926), pepsin (1932), ribonuclease (1936), deoxyribonuclease (1938) and the amylases (1948–51). Every enzyme has a complex composition and arises almost always from the union of two components, one called *apoenzyme* and the other *coenzyme.*

The apoenzyme is proteinous in nature. The coenzyme may be constituted by metals (iron, calcium, manganese, magnesium, etc),

(1) *Extract from a speech by Jules Lemaître on the occasion of the admission of Marcellin Berthelot into the French Academy, 2nd May 1901.*

(2) *On the subject of enzymes, see Volume I, the chapter entitled 'A Chain of Chemical Reactions'.*

by complex mineral and organic substances (vitamins), or by combinations of metals and organic substances (haems). It can happen that apoenzyme and coenzyme unite only at the moment when the enzymatic reaction is about to occur; and prior to this they remain apart although in the same medium. However, there are also cases where the two components appear to be practically indissociable. The coenzyme must then be regarded as the prosthetic group of an heteroprotein, the protein group being the apoenzyme.

Any enzyme, no matter which, exists to attack specifically a given substance called the *substrate.* The first step in this attack is that of enzyme-substrate combination, which since 1900 has been the subject of innumerable researches. On the chemical plane, particular study has been made of the nature of the reacting coenzymes (vitamins, nucleotides, etc), of the chemical groups responsible for enzyme-substrate combinations (sulphydril, amine and hydroxyl groups, etc), and of inhibition by substances blocking these reacting groups (complex metals). On the physical plane, it has been possible to specify the kinetics of the reactions—even those involving an activator or a secondary substrate—as well as the energetics of the reactions, the transfer of electrons, etc.

At the present time, several important problems appear to dominate the whole of enzymology. For example:

1. The nature of the enzymatic reactions which ensure the regeneration of high-energy phosphorylated derivatives (ATP). These reactions represent the energetic source used by the cell to initiate anabolic phenomena (synthesis of proteins, etc).

2. The nature of the nucleotides which participate, either as coenzymes (coenzyme I, II, A) or as acceptors of chemical groups ($H_3PO_4$, $-NH_2$, $-SO_4$, etc) which are transported by transferases from one molecule to another.

3. The structure of the enzyme molecules which are responsible for specificity, the amino acids which take part in the constitution of the polypeptide chains and the linkages between these chains.

4. The role of metals constituting part of the enzyme molecule (metallo-enzymes) or of its prosthetic group (haem) in the transfer of electrons.

This is just a glimpse of the many topics of interest in past and present-day enzymology. The growing complexity of the subject may be illustrated by a concrete example. A hundred and fifty years ago it could have been stated quite simply that cane sugar yields alcohol and carbonic acid by diastasic hydrolysis (there was a time when the word diastase designated all enzymes). In 1961, the statement would have been worded thus: sucrose (or any other substance able to provide glucose) yields ethyl alcohol and carbonic acid; but it yields these only when a chain of ten reactions has taken place. The nature of these ten reactions has now been elucidated.

## *Vitamins*

Like enzymes, vitamins are biocatalysts and powerful ones at that. It is known, as mentioned above, that vitamins frequently enter into the structure of coenzymes.

From the time of its formation, each cell receives the enzyme equipment it needs. Vitamins, however, are not elaborated by man's cells and are thus necessarily obtained from food. Should the diet become deficient in vitamins, disturbances which are named hypo- or avitaminoses soon become manifest.

Scientifically speaking, an exact knowledge of these disturbances dates back only to the beginning of this century, but it may be said that humanity has had a presentiment of the existence of vitamins for a long time. Even in ancient times, essential 'qualitative' foods were recognized. In order to fight against scurvy, the Vikings took the precaution of carrying onions in their ships, to be eaten raw. In 1667, Admiral De Ruyter carried fresh lemons in the store-rooms of his vessels. Captain James Cook kept his ships' crews free from scurvy by giving them fermenting malt and sauerkraut.

The scientific era succeeded the empirical era with the work of Gustav von Bunge. In 1881, a student of his, Lunin, put forward the hypothesis that milk must contain, in addition to casein, fat, lactose and salts, substances which are completely indispensable to nutrition. In 1891, Socin, a student of the same school, declared: 'Our first task will be to search for this or these substances in milk or in egg yolk'. The idea gradually took shape, and was finally adopted by Hopkins (1906), Stepp (1909), Osborne, Mendel (1911) and MacCollum (1913). In 1911, Funk proposed the name *vitamins* for these complementary or supplementary foodstuffs.

Today, two groups of vitamins are distinguished by their solubility characteristics. One group is called *fat-soluble* (vitamins A, D, E and K), and the other *water-soluble* (B and C). Vitamins A and D appear to be indispensable only for animals. The others (E, K, C, B) seem to be indispensable in both the animal and vegetable kingdoms. They make up part of the normal equipment of living cells. All the known vitamins, with the exception of vitamin $B_{12}$, can now be synthesized.

*Vitamin A* is necessary for the normal functioning of mucosae and plays an essential part in vision.

*B vitamins.* Many of these are already known and each one has a particular role. Thiamine cures beri-beri and occurs in rice-bran, beer-yeast, etc. Riboflavin, found in milk and egg-white, reduces certain kinds of dermatitis. Nicotinic acid (present in yeast, liver, meat) cures pellagra. Pantothenic acid, in the form of coenzyme A, takes part in numerous highly important metabolic reactions. Also classed as B vitamins are pyridoxin, biotin, folic acid, lipoic acid, and cobalamine (also called vitamin $B_{12}$, anti-pernicious vitamin, extrinsic factor, etc).

*Vitamin C* is ascorbic acid, lack of which is known to cause scurvy. The *D vitamins* are the antirachitic vitamins. In organisms deprived of the *E vitamins* (tocopherols), sterility in the female and cessation of spermatogenesis in males is observed. Finally, the *K vitamins* are necessary for the synthesis of prothrombin, a protein taking part in the formation of fibrin, of which blood clots are composed.

The science of vitamins is still young and is continually expanding. In the laboratory, it tends to become linked more and more closely with the science of enzymes (hence the importance of coenzymes). The use of these catalysts in medicine grows increasingly and could almost be called fashionable. Who has not been advised to take vitamin $B_{12}$?

## Hormones

The word hormone (which comes from the Greek *hormao*—'I excite'), was coined by Starling in 1905 to denote substances which stimulate certain functions. The existence of such substances was already known—or at least suspected—through the work of Brown-Séquard, of Vassale and de Gley, of Takamine and Aldrich, and of Bayliss and Starling. It was known that the substances are secreted by special glands in the organism (called by Claude Bernard, glands of internal secretion), the secretion being poured directly into the blood stream.

The concept of hormones, like that of vitamins, was destined to become very fruitful and many have now been discovered. The principal hormone-producing glands in man and vertebrates are the hypophysis or pituitary gland, the pancreas, parathyroids, thyroid, placenta, suprarenals, testes and ovaries. Their principal hormones are vasopressin and oxytocin, secreted by the posterior lobe of the pituitary; ACTH, FSH and LTH (or prolactin) elaborated by the anterior pituitary; and thyrotropin, produced by the intermediate lobe of the pituitary.

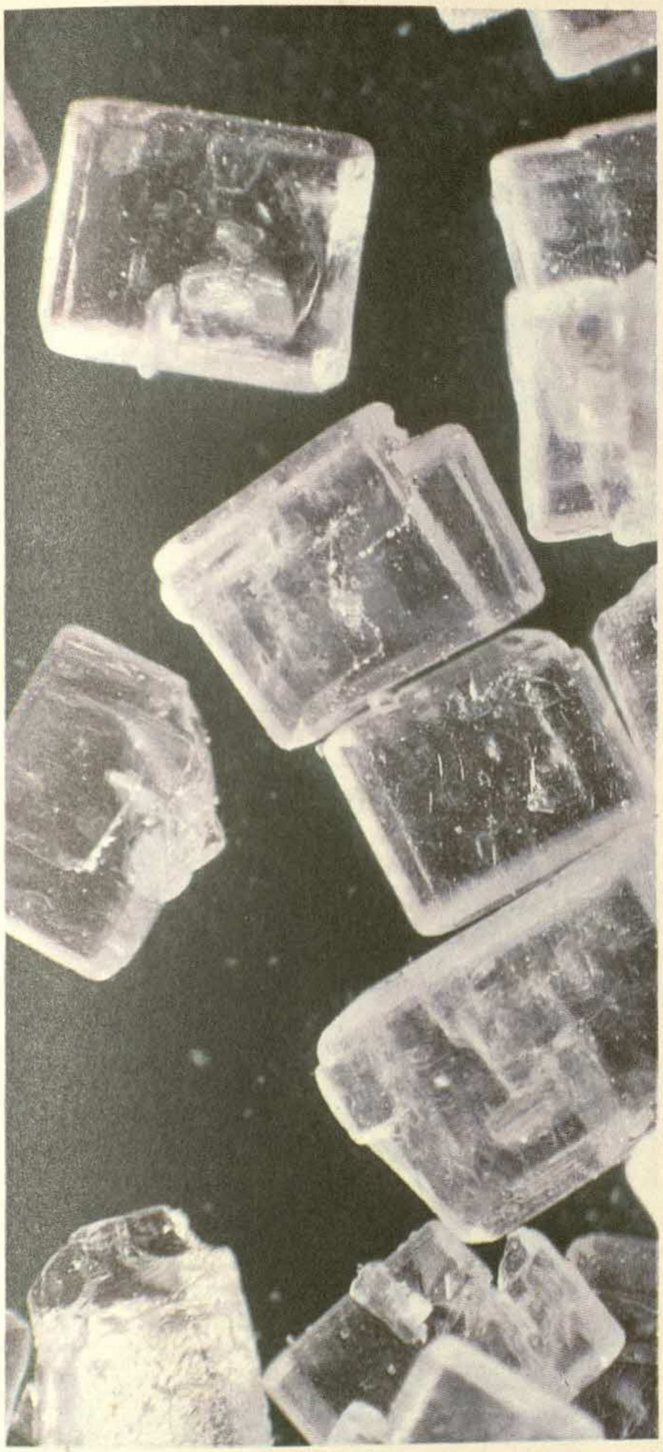
Insulin and glucagon are produced by the pancreas, and parathyroid hormones by the glands of the same name. The medulla of the suprarenal gland secretes adrenalin, while the cortex produces cortisone and aldosterone. The testes are the source of androsterone and testosterone. The ovaries produce oestrone, oestradiol and progesterone.

Chemically, three main groups of hormones may be distinguished. These are the *steroid hormones* (oestrogens, progesterone, androgens and cortico-suprarenal hormones), the *aminophenols* (adrenalin, thyroxin), and the *protein hormones*, which have been extensively studied in the last few years.

The effects produced by hormones are at the same time varied, numerous and of enormous importance. These substances have a profound effect on morphology and determine the sexual characters and also the growth of vertebrates. They bring about metamorphosis of amphibians and also moulting and metamorphosis of insects. We may mention their role in colour-change and in the processes of innumerable metabolic reactions (basic metabolism, metabolism of minerals, glucose metabolism). Again, hormones are essential for the reproductive functions and they also regulate behaviour (psychism, instinct). At least in part, they control the nervous system. They nearly always act at a distance from the point at which they were liberated. The cells which are sensitive to hormones are termed *receptors*.

The problem of hormones, of prime importance to the physiologist, also deserves the close attention of the physician, for many diseases, often serious ones, result from the hypo- or hypersecretion of these substances. Such are Addison's disease (atrophy of the suprarenal cortex), pancreatic diabetes (destruction of the pancreatic islets which normally secrete insulin) and Basedow's disease, due to hyperfunctioning of the thyroid. All these diseases, however, can be alleviated by special treatment.

Several chapters on hormones will be found in this book and they will complement this necessarily schematic account.



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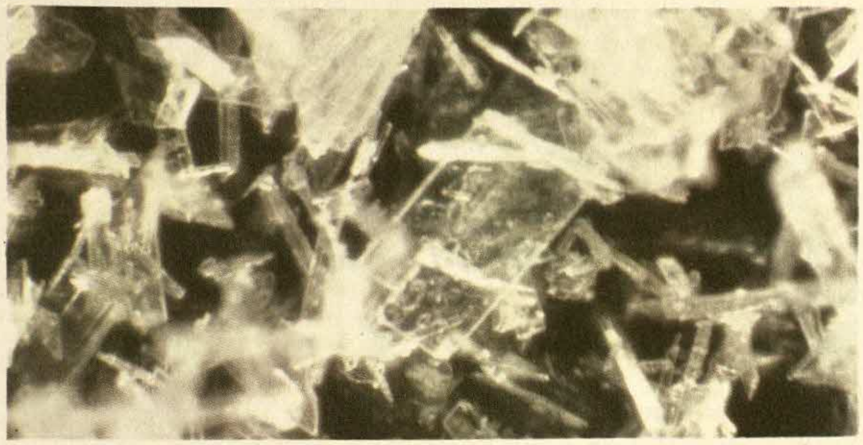
# *Vitamins*

*Vitamins too are chemical substances indispensable to the functioning of our bodies, but unlike hormones, they come to us from outside, by means of our food. The pictures on the right show, from top to bottom, the crystalline form of vitamin $B_1$ (anti-neuritic vitamin); vitamin $B_{12}$ (anti-anaemic vitamin); vitamin $B_6$; and folic acid. Above is shown vitamin C (ascorbic acid). (Photographs by Lod, taken at the Société des Usines Chimiques, Rhône-Poulenc, France).*



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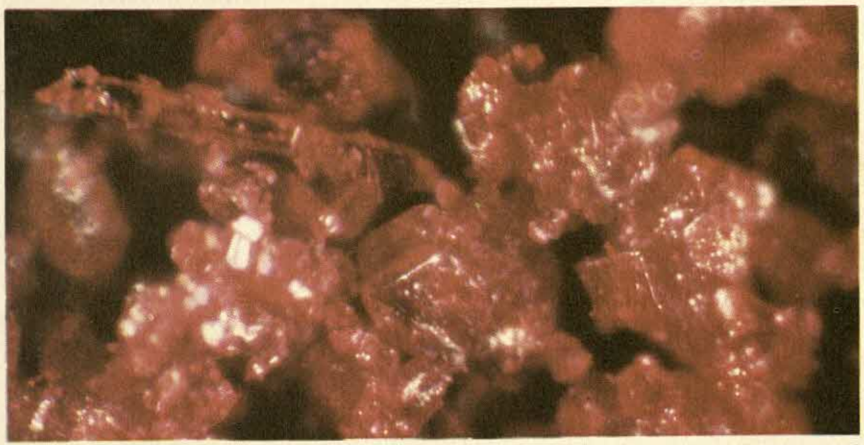

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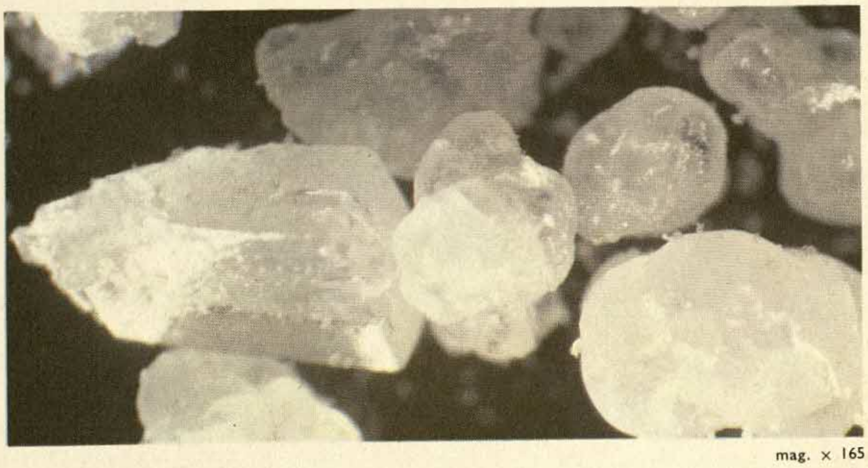

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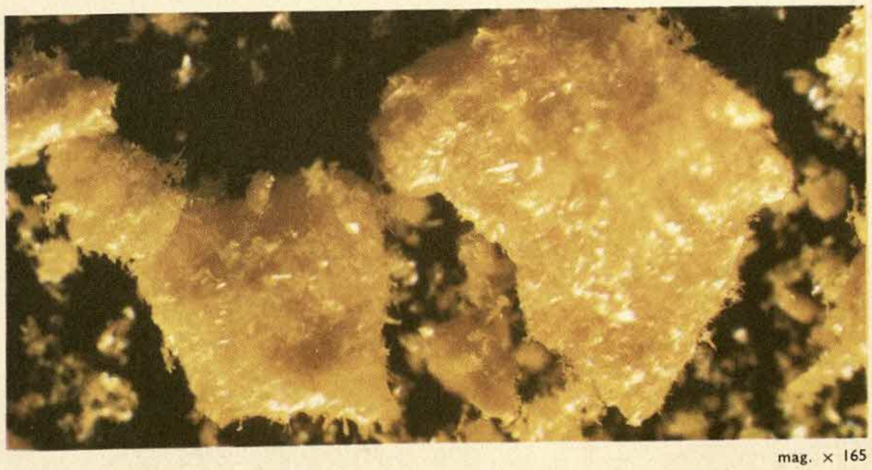

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# Hormones of the suprarenal cortex

*Marc CANTIN and Pierre JEAN*

*The hormonal substances elaborated in the outer part of the cortex of the suprarenal glands play an extremely important role in the functioning of the body. These two small, yellowish-brown glands, lying flattened above the kidneys, weigh only a few grams, yet they are as necessary to man as his liver. Their secretory products are poured directly into the blood stream, which is why they are called endocrine glands, or glands of internal secretion.*

When a suprarenal is opened, two regions are visible: the central part, called the medulla, which secretes adrenalin; and the other, the peripheral or cortical region, which secretes the steroid hormones, so called because of their chemical relationship with the sterols. The steroid hormones fall into three main groups: the corticoids[1] proper, the folliculoids,[2] and the androgens.[3]

More than thirty different hormones have been isolated from the suprarenal cortex, and their elaboration in such a small gland is truly amazing. The synthesis of these products is very complex and implies a whole series of enzymatic mechanisms. The majority of the secretions are known to be derived from cholesterol, which occurs in the gland in quantity.

By means of the hormone corticotrophin, the hypophysis[4] controls production of the glucocorticoid[5] hormones (cortisone, hydrocortisone). The secretion of corticotrophin itself is believed to be controlled by the hypothalamus and autonomic nervous centres. Regulation of the secretion of mineralocorticoid[6] hormones is even more complex and seems to be dependent on the pineal body and on the level of sodium and potassium in the blood. Almost nothing is known of the regulation of secretion of sex hormones by the cortex, except that their blood level rises under certain pathological conditions of the gland.

The suprarenal cortex is essential to life and if it is destroyed (Addison's disease), death rapidly ensues. The cortex affects a long sequence of biological phenomena. To take one of Carrel's figurative illustrations, if the substances produced by this gland were blue, the whole organism would be tinged with blue, the blue tinge being most intense in the suprarenal glands.

## Hormones and metabolism

The glucocorticoids, as their name indicates, regulate the metabolism of sugars. Suprarenalectomy is followed by hypoglycaemia,[7] accompanied by a decrease in the glycogen[8] stores in the liver and muscles. In a diabetic animal, ablation of the gland also produces a decrease in blood sugar. The mineralocorticoids (deoxycorticosterone, aldosterone) for their part, regulate the balance of water and certain electrolytes, sodium and potassium in particular.

After ablation of the cortex, an excessive elimination of sodium in the urine occurs. This phenomenon is accompanied by a drop in blood sodium and a decrease in volume of the blood plasma. Dehydration of the organism results, but it is a curious fact that the cells themselves have a greater affinity for water at that time.

When mineralocorticoids are administered, an opposite state of affairs is produced, with retention of sodium and exaggerated urinary secretion of potassium.

The corticoid hormones have an influence on inflammatory phenomena. The mineralocorticoids have a prophlogistic action, whereas the glucocorticoids have an antiphlogistic one.[1] The antiphlogistic action of cortisone and hydrocortisone is made use of in the treatment

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(1) Corticoids: *substances that stimulate the activity of the suprarenal cortex.* Antiphlogistic corticoids: *corticoids with an anti-inflammatory action.* Prophlogistic corticoids: *corticoids which facilitate inflammation.*

(2) Folliculoids: *compounds with hormonal activity analogous to that of the secretory products of the ovarian follicle.*

(3) Androgens: *compounds with hormonal actions of testicular type (testoids, male hormones).*

(4) Hypophysis: *a small endocrine gland, below the brain, encased in the bones at the base of the cranium.*

(5) Glucocorticoids: *corticoids which stimulate an increase in liver glycogen and in the level of blood sugar (eg, cortisone, hydrocortisone).*

(6) Mineralocorticoids: *corticoids which favour the retention of sodium and the elimination of potassium by the kidneys.*

(7) Hypoglycaemia: *a decrease in the quantity of glucose in the blood.*

(8) Glycogen: *a storage substance which is stored in the organism and can be turned into sugar as needed.*

(9) Specific resistance: *resistance to a given agent, acquired by prior exposure to the same agent.* Aspecific resistance: *resistance to a given agent acquired by prior exposure to a different agent.*

(10) Mithradatism: *immunity from a poison induced by administering gradually increased doses of it.*

of many pathological conditions in which an inflammatory reaction is not desirable. These hormones do not act on the pathogenic agent but on the reactivity of the tissues in the presence of the agent.

The sex hormones (androgens and folliculoids) secreted by the cortex have a supplementary role governing the growth of facial, axiliary and pubic hair in man.

If the role of the suprarenals is of fundamental importance during the normal course of life, it is even more so in time of emergency or, in modern terms, of stress and in the processes of adaptation.

## *Regulation of the internal medium*

Claude Bernard had already drawn the attention of biologists to the importance of the regulatory systems of the internal medium before Cannon gave these phenomena the name of 'homeostasis' and opened interesting perspectives of the manner in which they operate. In particular, he demonstrated the role of the autonomous nervous system and the part played by the suprarenal medulla in reactions in emergency.

A theory encompassing wider horizons was put forward by Selye in his concept of systemic stress and diseases of adaptation. He made a vital distinction between the specific effects and the non-specific effects produced by a given stimulus.

For example, Selye observed that cold, which is a specific vasoconstrictor, and heat a specific vasodilator, have other effects in common which can be produced by the most varied stimuli, such as muscular exercise, exposure to x-rays, and disease. These effects are manifested by a group of three symptoms: increase in volume of the suprarenal cortex, involution of the thymo-lymphatic organs, and gastric ulcers. To this syndrome Selye gave the name stress, which he defined as the sum of all changes induced non-specifically in a biological system. All stimuli able to produce such changes were called 'stressing agents'.

Increase in volume of the suprarenal cortex corresponds to a greater activity in each of its cells. A much greater quantity than usual of suprarenal hormones is secreted during stress and these play an indispensable part in maintaining homeostasis. They liberate stores of energy normally held in reserve or used for other functions (such as digestion, anabolism).

Subsequent experiments have shown that the appearance of gastric ulcers during the course of stress does not depend on the suprarenal hormones, but that thymo-lymphatic involution is connected with the overproduction of these hormones.

Selye showed that the response of the suprarenals depends on the hypophysis. Adrenocorticotrophic hormone (ACTH) which is secreted in large quantities during stress, stimulates the suprarenal.

The functioning of the nervous mechanisms, of the hypothalamus in particular, which are believed to govern the activity of the hypophysis during stress, is still being studied.

This identical response to different stressing agents has a characteristic pattern called the 'general syndrome of adaptation'. This syndrome comprises three stages: first, the alarm reaction, including an initial shock phase followed by a counter-shock phase, during which the mechanisms of adaptation begin to operate; the resistance phase, when the adaptive responses are optimal; and lastly, a phase of exhaustion, which marks the loss of the acquired adaptation.

Research on stress has shown that the adaptive phenomena, normally necessary to life, can cause disease. Work over the past twenty-five years has shown that in the presence of so-called conditioning agents, the application of a stressing agent or the administration of corticoids can produce most varied diseases in animals. It is now more and more widely believed that a large number of illnesses are due to a number of pathogenic factors or conditioning agents, and not to a single agent. This is an excellent illustration of Pasteur's famous phrase, 'Le microbe n'est rien, le terrain est tout' ('The microbe is nothing, the environment is everything').

The most recent and probably the most promising field of research is that of the protection afforded by stress in several experimental diseases. This protection is called 'aspecific resistance', in contrast to 'specific resistance',[9] illustrated by mithradatism.[10] Thus, if animals are previously submitted to the stress of forced muscular exercise, to cold baths, or surgical operations, they become resistant to toxic agents or to pathogenic conditions which would normally produce the most varied lesions. Knowledge of the protective mechanisms acquired through stress will without doubt provide a basis for the discovery of new therapeutic weapons.

All this research throws new light on the participation of hormones not only in affections of the endocrine glands, but in disease in general.

### HISTORICAL NOTES

1856
BROWN-SÉQUARD *removed the suprarenals for the first time and concluded that these glands are necessary to life.*

1925
*Suprarenalectomized animals were kept alive by injections of suprarenal cortex extract (and it was established that these animals, deprived of their suprarenals, succumb rapidly in situations of 'stress').*

1933
*The first crystalline fractions possessing high corticoid activity were isolated* (GROLLMAN, KENDALL, REICHSTEIN). *Also, doctors observed the alleviation of arthritis in women during pregnancy, a period when the production of cortico-suprarenal hormones increases.*

1936
SELYE *discovered the 'general syndrome of adaptation'.*

1937
*First synthesis of a corticoid, deoxycorticosterone, from stigmasterol* (STEIGER *and* REICHSTEIN).

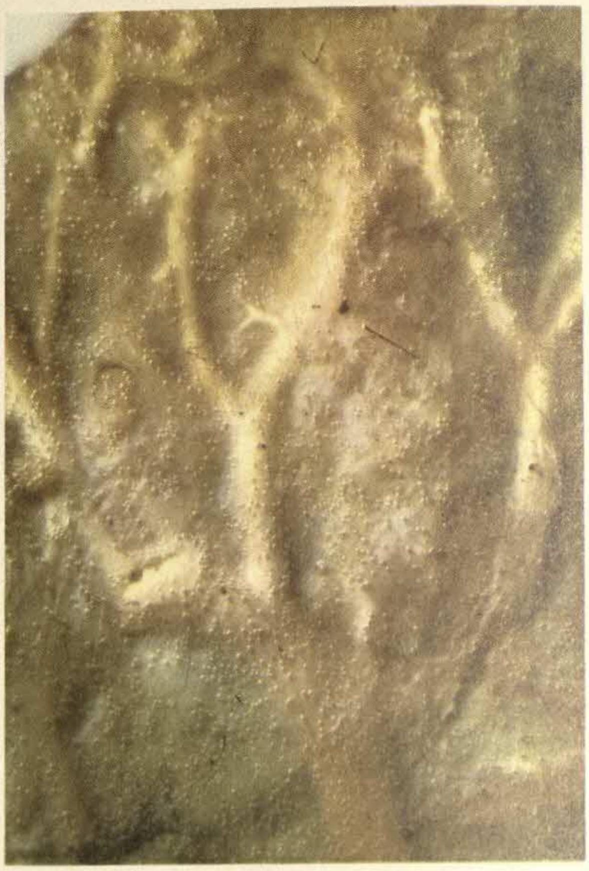
1949
HENCH *used cortisone successfully on patients with rheumatoid arthritis, a chronic disease of the joints.*

1955
*A chlorine atom was introduced into the glucocorticoid molecule and increased its anti-inflammatory activity.*

1956
*Alterations of the molecular structure of corticoids resulted in the new synthetic products, prednisone and prednisolone.*

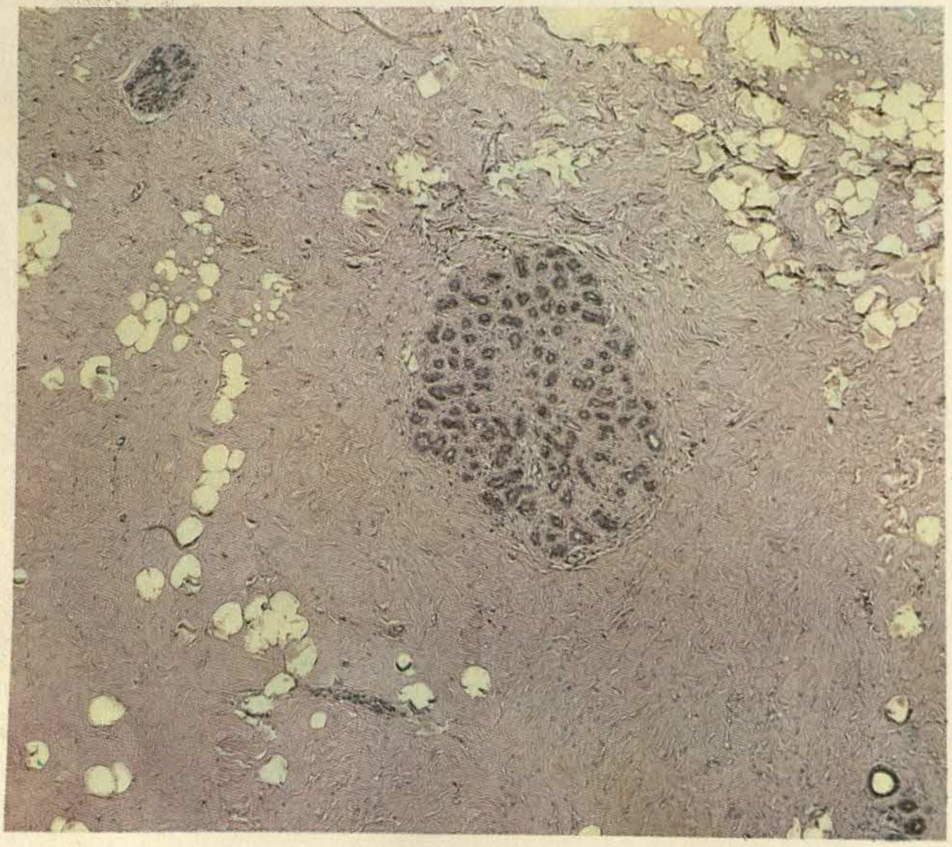
1957
*A new mineralocorticoid, aldosterone, much more powerful than deoxycorticosterone, was isolated.*

1958
*Discovery of substances of the spirolactosteroid family, capable of blocking the activity of mineral-ocorticoids.*



# Lactation

*In order that the mother can nourish the new-born infant, a temporary change brought about by certain hormones (p. 59) is produced during gestation. The mammary tissue (photographs below) hypertrophies; certain ducts (photograph above, right) convey the milk to the nipple of the breast. (Photographs by Lod, taken in the laboratory of Professor Jean Gosset, Hôpital Saint-Antoine, Paris; preparations by Madeleine Boucher).*



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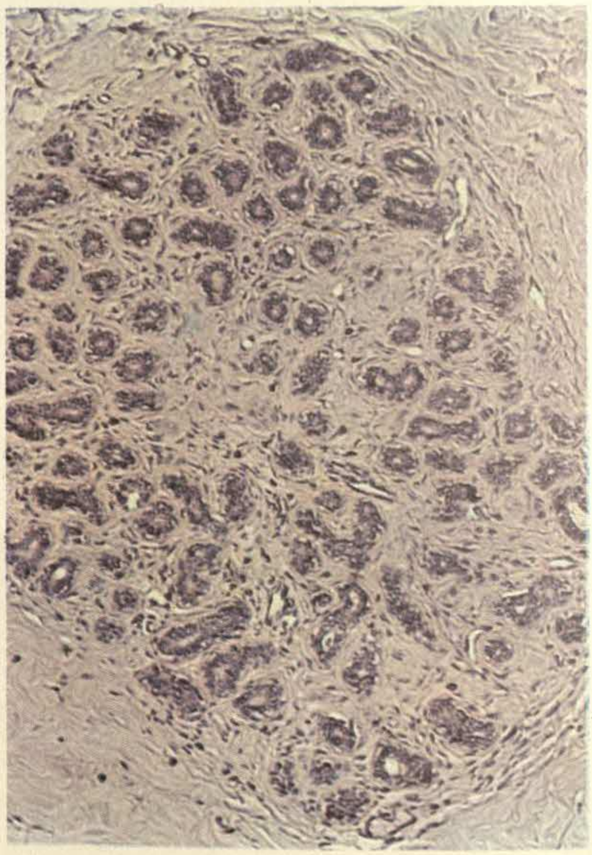

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# Sex hormones

## *Michel ALBEAUX-FERNET*

*In the extensive and supple range of the hormonal regulation of the human machine, the hormones associated with the physiology of the sex organs occupy a key position. Although of varied chemical nature, these hormones all belong to the great group of steroids. Those occurring in particularly large quantities in females are called oestrogens (oestrus, period of 'heat'); those predominating in males are called androgens.*

Substances which can produce phenomena in the tissues of the vagina, uterus and mammary glands (fig. 1) of ovariectomized or senile females, analogous to those accompanying spontaneous oestrus,[1] are denoted by the name oestrogens.

The ovary is the principal source of oestrogens, the quantity of which is decreased after ovariectomy;[2] it stores very little, however, since enormous quantities of ovaries are required for the extraction of very small amounts of oestrogens.

The secretion is essentially from the thecal gland of the ovary, which comprises not only the internal layers of active follicles and corpora lutea[3] but also the layers of numerous atretic follicles, by which a permanent secretion of oestrogens is ensured.

The suprarenals are also a source of oestrogens, produced in the reticulated zone, but the importance of this is still a matter for discussion (see the preceding chapter).

In a pregnant woman the placenta[4] plays a not inconsiderable part in the formation of oestrogens.

## *Properties and actions of oestrogens*

The oestrogens comprise steroids with eighteen carbon atoms, of which the most important, in decreasing order of activity, are oestradiol, oestrone or folliculin, and oestriol. Through metabolism certain of these substances can be converted from one to another: oestradiol changes to oestrone by a reversible reaction, whereas the degradation of oestrone to oestriol is irreversible. This is one of the processes of inactivation of oestrogens; others are oxidation, conjugation, reduction, and even transformation into other steroids.

The receptor organs (uterus, vagina and mammary glands) and progesterone (secreted by the corpora lutea) influence the mechanism and direction of these inactivations, but the liver plays the principal role.

Oestrogens are eliminated in bile and 30 per cent of the oestrogens thus eliminated pass into the intestinal tract. The remaining 70 per cent can be reabsorbed in the duodenum. Most of the oestrogens, however, are eliminated in the urine; analysis of their urinary metabolites determines only imperfectly the amounts secreted, whether the method used is biological or chemical.

Oestrogens are endowed with two essential physiological properties: genital and metabolic.

They act on the vaginal mucosa, causing a proliferation of the cells and their maturation and keratinization,[5] which can be recognized clinically by studying vaginal smears. The layer to which the sloughed vaginal cells belong, and the degree of maturation which they have reached in the course of the menstrual cycle, may be seen by the morphology of the cells, their staining reaction (acidophilic index) and the character of the nucleus (pycnotic index).

Oestrogens stimulate secretion from the cervical glands in the neck of the uterus and cause the production of an abundant, translucent glair; the study of this on the fourteenth day of the cycle is important in gynaecology.

In the body of the uterus, the oestrogens evoke proliferation of the endometrium,[6] which can be studied by biopsy.[7] During the first phase of the cycle, which depends solely on

(1) Oestrus: *the group of physio-biological phenomena characterizing the various stages of sexual excitement in female mammals.*

(2) Ovariectomy: *ablation of one or both ovaries.*

(3) Corpus luteum: *when the ripe Graafian follicle has ruptured and the ovum within it has escaped, the cells of the follicle wall undergo an important transformation, and the whole forms a small organ (a true gland of internal secretion), the* corpus luteum *(yellow body), which exists for only 14 days of the 28-day cycle.*

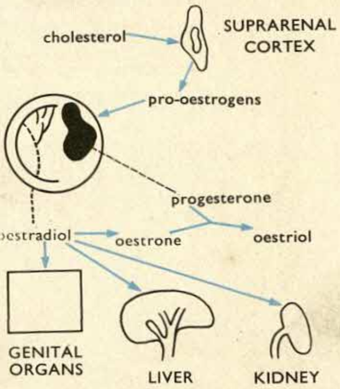


*Fig. 1. The sex hormones are derivatives of cholesterol and in women are secreted by the ovary. The oestrogens are produced continuously; progesterone is secreted by the corpus luteum. These hormones cause changes in the reproductive organs; they act on the liver, where they are metabolized, and on the kidney, by which they are eliminated.*

oestrogen secretion, there is an intense cellular proliferation and multiplication and the epithelium forming the glandular tubes sinks down in the endometrium. During the course of the second half of the cycle, the oestrogens exercise their effects jointly with progesterone; the endometrium assumes a secretory aspect, for it becomes filled with glands whose cells are rich in glycogen and the lumina of which dilate.

The oestrogens appear to act on the metabolism of proteins and fats, and their presence determines the distribution of adipose tissue in women.

Above all, the oestrogens have the property of retaining water in most of the tissues and they affect calcium metabolism, as witnessed by numerous clinical observations and the study of variations in the amount of calcium.

During the active sexual life of a woman, the oestrogen level exercises considerable influence on the structure and function of the anterior pituitary. Oxidized products, resulting from oestrogen degradation in the liver, appear to play a role in determining the nature of gonadotrophic[8] substances liberated from the anterior pituitary. A slight secretion of oestrogens causes the anterior pituitary to produce a secretion predominant in FSH, while a hypersecretion of oestrogens elicits an excess of LH. In this way the various phenomena constituting the menstrual cycle take place.

The development of synthetic oestrogens by the pharmaceutical industry in the form of inexpensive pills has made such active substances as ethinyl-oestradiol, diethylstilboestrol, hexoestrol and dienoestrol available to the physician. These compounds can be administered orally, since they are not inactivated by the liver.

Carefully administered under close supervision, these synthetic oestrogens produce remarkable results in cases of oestrogenic insufficiency occurring in atrophy of the reproductive organs, and in the oestrogenic deficiency from which the majority of menopausal disturbances originate.

In man, these same substances have proved to be of remarkable efficacy in cases of cancer of the prostate, although the effect is only temporary.

## The effects of progesterone

Progesterone is the hormone which causes the uterine mucosa, previously made hyperplasic by the oestrogens, to change to the gravidic endometrium,[9] thus permitting implantation of the fertilized egg.

Progesterone has a double origin: the suprarenal glands and the ovaries. It is not possible to determine the amount produced by the suprarenals, but most of the progesterone is ovarian, being secreted by the corpus luteum. This secretion has a character unique in endocrinology in that it is intermittent, being produced only in the second part of the menstrual cycle.

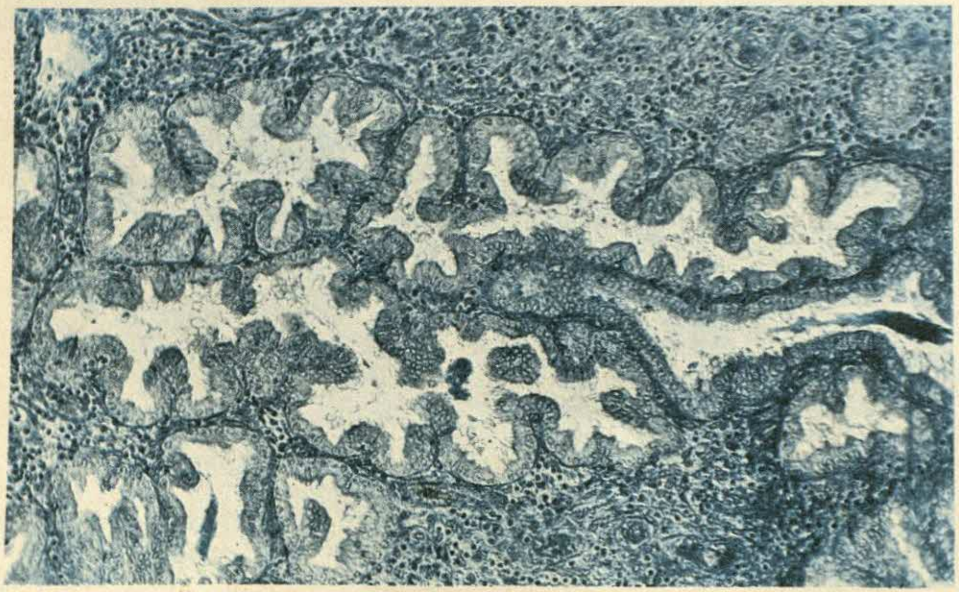
During this time, progesterone complements the action of oestrogens on the uterine mucosa, which is brought to its progestative condition, it enhances the metabolism of oestrogens in the uterus, and contributes to the renal elimination of oestrogens.

Converted in the endometrium, progesterone is eliminated in the form of pregnandiol in the urine. The excretion of pregnandiol begins the day after ovulation, increases to a level of 5 to 8 mg and then slowly decreases until the day before menstruation.

Progesterone is endowed with two types of physiological properties: genital and metabolic. It initiates the development of plicate cells[10] in the vagina. In the uterus it softens the myometrium,[11] inhibiting its contractions and, acting synergically with the oestrogens, prepares the mucosa for implantation. It also reduces the peristaltic[12] activity of the Fallopian tubes. Still in synergy with the oestrogens, progesterone causes the mammary glands to hypertrophy by stimulating development of the gland cells.

Progesterone has the property of raising

*Fig. 2. Section of uterine endometrium in the progestational phase (from 14th to 21st day).*



(4) Placenta: *nutritive organ specially developed by the mammalian foetus, which becomes attached to the wall of the maternal uterus, ensuring the nutrition and respiration of the embryo.*

(5) Keratinization: *modification of the outermost cells of the vaginal mucosa which become enriched with a special chemical substance, keratin.*

(6) Endometrium: *uterine mucosa.*

(7) Biopsy: *surgical removal from a living subject of a fragment of tissue or organ, in order to analyze or examine it.*

(8) Gonadotrophic substances: *substances which initiate or stimulate the activity of the sex glands or gonads, such as* FSH *or follicostimulin, and the hormone called* LH *or* ICSH.

(9) Gravidic endometrium: *designates the uterine mucosa (endometrium) modified by pregnancy (the uterus is termed gravid when it contains an embryo).*

(10) Plicate cells: *cells which are folded back on themselves.*

(11) Myometrium: *uterine muscle.*

(12) Peristalsis: *a special type of contraction occurring in the smooth muscles of hollow viscera, which habitually serves to force along or evacuate the contents of these (intestine, stomach, uterus).*

the body temperature, as clearly demonstrated (fig. 3) by a rise in rectal temperature. The temperature is taken to the nearest 1/10° in the morning on waking and the rise in temperature observed is of great importance in the study of sterility, for it proves the existence of a functional corpus luteum.

Synthetic progesterone is active only by injection, but a closely related substance, anhydroxyprogesterone, is active when taken orally.

## *Androgens*

Androgens are steroid hormones responsible for sexual characters in man.

In men, a third of the total secretion is produced by the testes and the rest by the suprarenal cortex. In women, the suprarenal gland is the only source.

*Testicular androgens* are secreted by the interstitial tissues of the testis, namely by the cells of Leydig. They act on many parts of the organism, and after being utilized, the essential hormone testosterone is partly inactivated by the liver, forming derivatives which belong to the 17-ketosteroid group. These derivatives are mainly androsterone, with reduced androgenic activity, and etiocholanolone, which has no androgenic activity.

The androgens of the suprarenal cortex are produced by its internal reticulated zone. They do not appear, however, to be produced by an autonomous mechanism proper to themselves, but are more probably by-products of the synthesis of suprarenal corticoids. Dehydroepiandrosterone and androstenedione are the main cortico-suprarenal androgens.

The metabolites of testicular and suprarenal androgens are eliminated in the urine in the form of 17-ketosteroids; many methods of fractionation have been suggested to determine both quantitatively and qualitatively the testicular and suprarenal steroids, for example, the digitonine method and chromatographic methods.

The physiological properties of the androgens may be grouped in three main categories: sexual activity, metabolic activity, and action on growth (figs. 4 and 5).

Until the age of eight years, androgenic secretion is virtually non-existent in both sexes, but at that age it first appears and then gradually increases to the normal level at about the age of twenty. It is a curious fact that the increase in androgens is much slower than the increase in oestrogens, where maximal secretion is at about twelve years of age. The increasing androgen level accounts for the differences that are observed among boys as to the age at which puberty begins. Puberty can indeed begin only when a certain equilibrium between the two groups of androgenic and oestrogenic hormones is reached.

Testosterone appears to be responsible for the appearance of the male secondary sexual characters and for their development, such as facial hair, the lozenge-shaped area of pubic hair, the development of the thyroid cartilage and the further development of the reproductive organs.

In both sexes, the androgens of cortico-suprarenal origin are possibly the ones responsible for lip and chin hair, axillary hair, and the triangular area of pubic hair in women.

The androgens play a considerable part in the anabolism of proteins. Under the influence of these hormones the nitrogen balance becomes excessive and, at the same time, a decrease of nitrogen and creatinine in the urine is observed.

In small amounts, the androgens cause a multiplication of the eosinophil cells of the pituitary, which secrete the growth hormone, stimulating the activity of the cartilages joining the bones.

Large amounts of testosterone, on the other hand, induce the fusion of these cartilages and consequently arrest growth.

During the course of their metabolism in the organism, the androgens appear to regulate production of stimulins by the pituitary, such as FSH which primarily affects spermatogenesis, and ICSH which acts on testicular endocrine secretion and seems also to control androgenic secretion by the cells of Leydig.

The therapeutic use of androgens devolves from the physiological properties which have just been described. Not only testosterone is used but also nearly-related substances which are rather less potent in producing the characters of masculinity, although their anabolic activity is retained. The most important of these substances are methyltestosterone and methylandrostenedione. In man their chief uses are for genital insufficiencies and retardation of growth.

In osteoporoses in both sexes remarkable results have been achieved through reconstructing the protein layer of the bones by the use of testosterone.

Lastly, it is known that the androgens have a remarkable effect on pain and general condition, especially in metastases of breast cancer, but unfortunately the effect is only temporary.

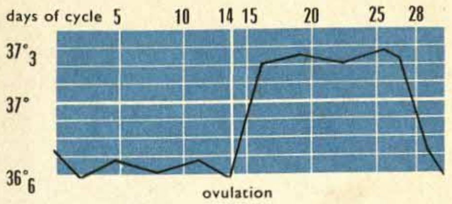


*Fig. 3. Temperature curve of normal menstrual cycle, showing low temperature in the first phase, rise in temperature at ovulation, high temperature in the second phase, and drop in temperature at menstruation.*

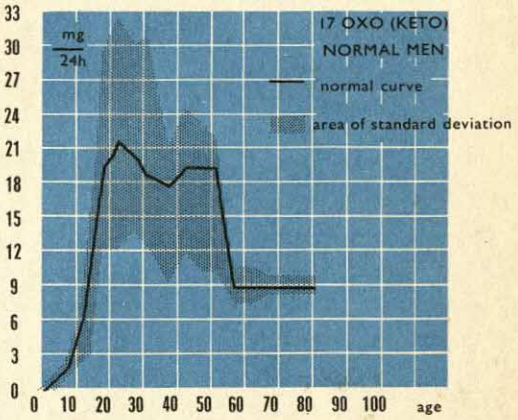


*Fig. 4. Graph of urinary elimination of 17 ketosteroids in men at different ages.*

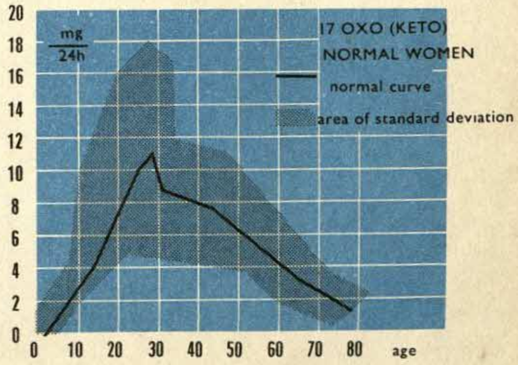
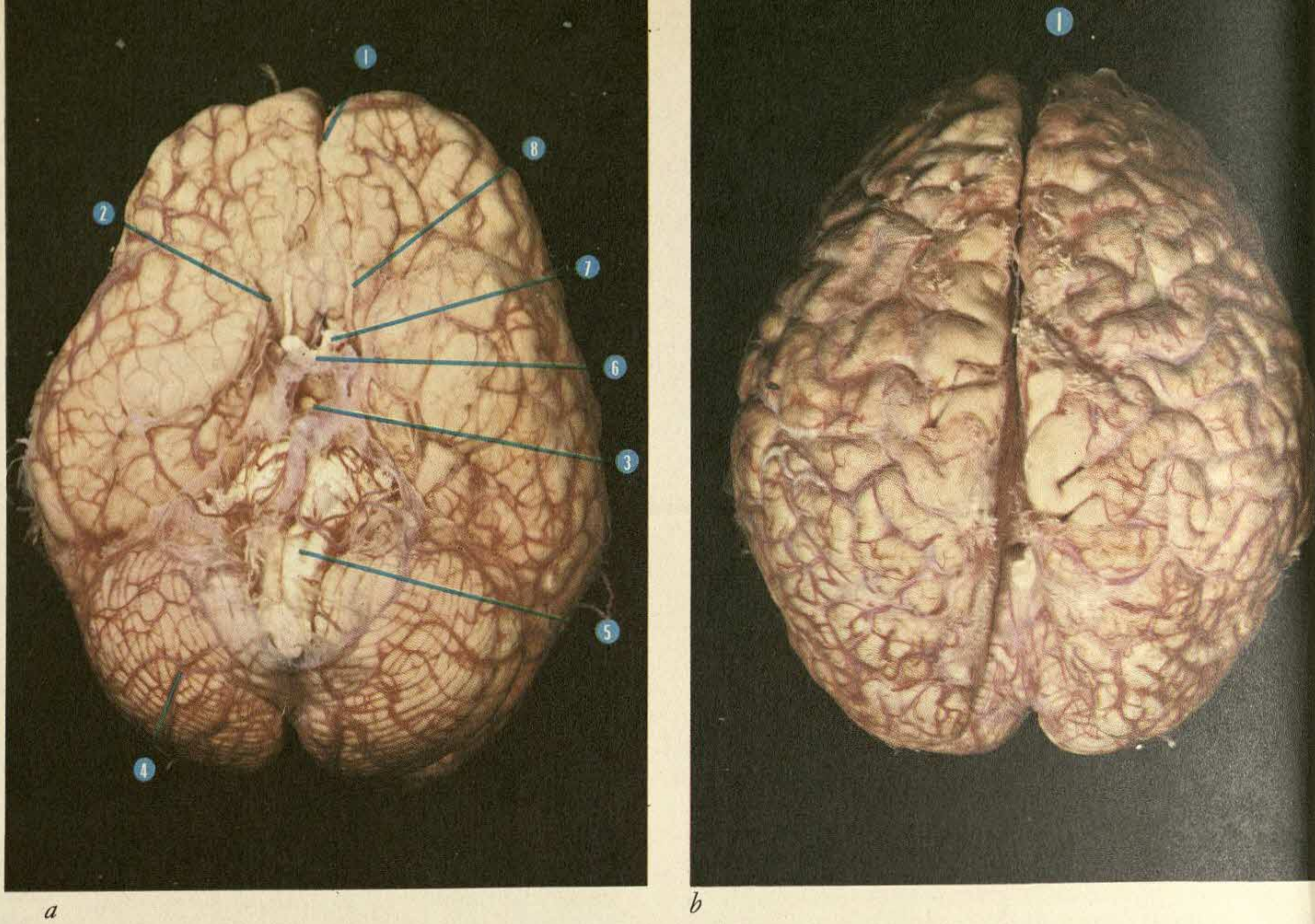


*Fig. 5. Graph of urinary elimination of 17 ketosteroids in women at different ages.*

1. interhemispheric fissure
2. Sylvian fissure
3. mamillary tubercle
4. cerebellum
5. cerebral peduncle
6. optic chiasma
7. optic nerve
8. olfactory peduncle
9. frontal lobe
11. temporal lobe
12. occipital lobe
13. parietal lobe
14. Rolando fissure
15. epiphysis



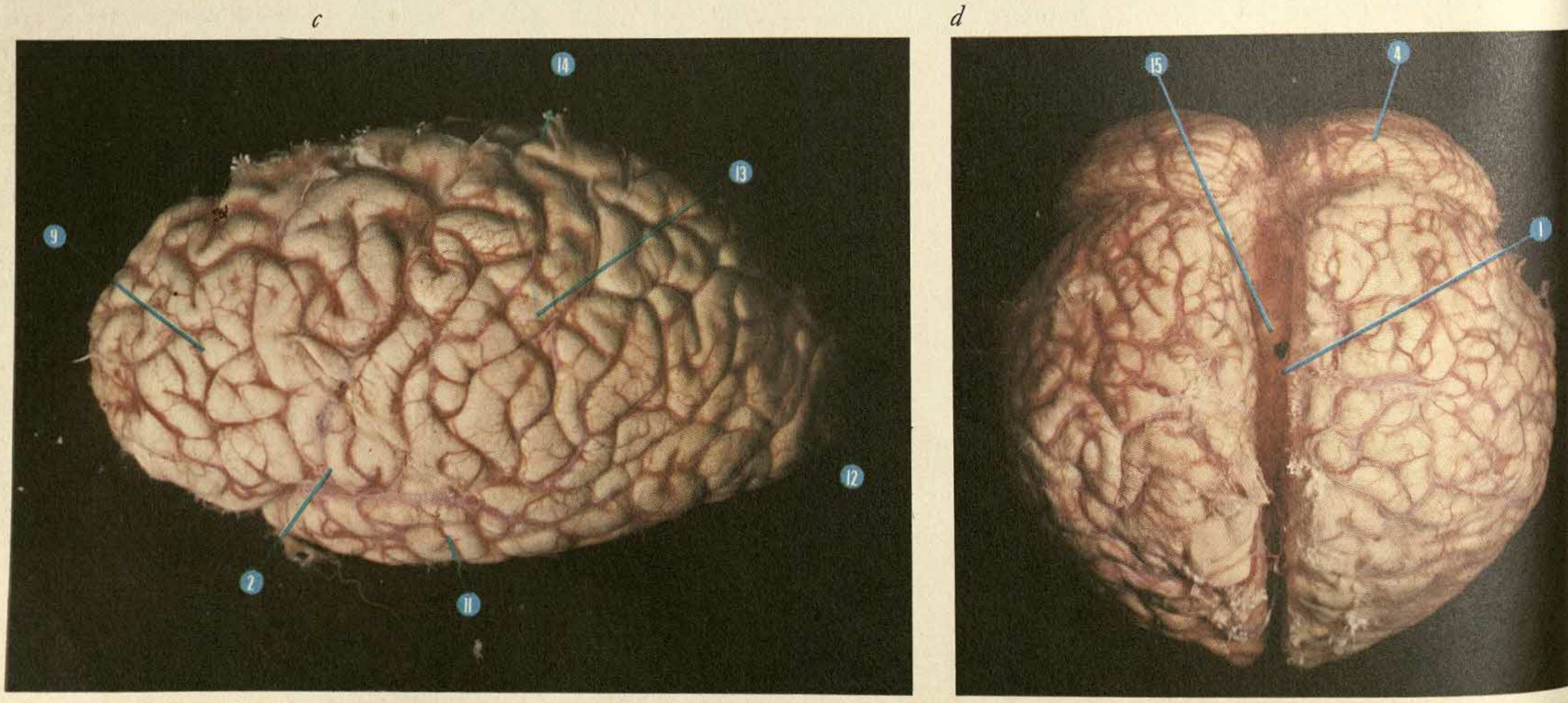
a

b

*The nervous system is the most important of all the main services which relate the different parts of the organism. The integrator of all the nerve functions is the brain, of which four distinctive aspects are seen here:* a, *lower view;* b, *view of the upper surface (meninges have been taken up slightly in the centre, and the cerebellum, which should be in the bottom part of the photograph, has been drawn back);* c, *side view of the left hemisphere;* d, *upper view—the cerebellum can be seen in the top part of the photograph (laboratory of Professor Kourilsky, Hôpital Saint-Antoine, Paris). The brain is the centre of an important electrical activity which can now be recorded by means of electrodes fixed on the cranium, as shown on the right. (Photos Lod).*

c

d



PART FOUR

# The nervous system

# The origin of the nerve impulse

Robert STÄEMPFLI

*Our understanding of the working of the nervous system has progressed in a spectacular fashion during the past twenty or thirty years owing largely to technical advances in the field of electronic equipment.*

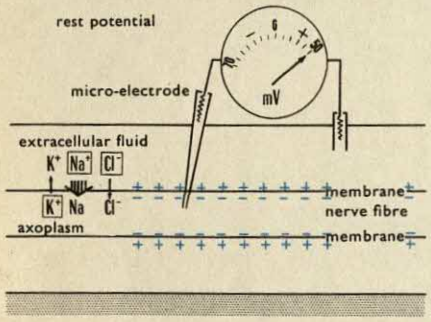


*Fig. 1. Diagrammatic representation of direct measurement of the resting potential of a nerve fibre by means of a microelectrode. The tendency of ions to diffuse across the excitable membrane towards lower concentrations is shown by arrows which are thicker or thinner according to the permeability of the membrane. It can be seen that at rest the membrane is only slightly permeable to sodium ions, but sufficiently permeable to potassium and chloride ions. The potential which results from these three piles of concentration connected in parallel is shown on the meter, one terminal of which is connected to the microelectrode and so to the axoplasm, and the other to the extracellular fluid.*

The latest advance in this field is due to the work of the English scientists Hodgkin, Huxley and Katz, and of the Americans Ling and Gerard. These scientists have succeeded in introducing a glass micropipette into the interior of an excitable structure, such as a nerve or muscle fibre, without impairing its property of excitability. As a result, one can now measure directly the absolute value of the difference in electric potential existing between the interior of the cell and the exterior (the tissue fluid, whose ionic concentration is similar to that of blood plasma). This experiment has confirmed the belief of the older neurophysiologists that there is a so-called 'resting' potential always present between the internal and external surfaces of the membrane separating the two media. The inside of the nerve fibre is about 70 mV negative in relation to the external solution, at the resting state.

## The resting potential

The resting potential disappears slowly after the death of the cell. One can make it disappear rapidly by replacing the extracellular fluid by a solution containing the same concentration of potassium ions as does the axoplasm.[1] This observation suggests that the resting potential is due to the greater concentration of potassium in the axoplasm compared with the external solution (fig. 1). Examples are known in physical chemistry of such potentials of concentration or of diffusion, occurring in relation to a membrane that is permeable to an ion which is in unequal concentration on the two sides. This difference in concentration is the origin of a movement of the ions, greater in one direction than in the other. In our case, the tendency of the potassium ions, which are positively charged, to leave rather than enter the fibre renders the interior of the fibre negative. The difference in potential thus occurring in relation to the membrane prevents the passage of ions in one direction from becoming more frequent than in the other.

There exists, therefore, an equilibrium in which, due to the membrane potential, the inflow and outflow of ions are equal. The value of the potential is directly proportional to the logarithm of the ratio between the ionic concentrations (Nernst's Law). In the nerve fibre this equilibrium is only an apparent one, since the liquids separated by the excitable membrane contain other ions which pass through the membrane more or less easily. Thus, chloride ions ($Cl^-$), for example, pass easily. They are found in low concentration in the axoplasm and the difference in concentration allows us to calculate a resting potential similar to that due to potassium (fig. 2).

Sodium ions are distributed in the opposite way. There are few in the interior and many in the exterior fluids. Their diffusion potential should make the interior of the fibre positive with respect to the exterior. Therefore it must be assumed that at rest the membrane allows so few sodium ions to pass that their diffusion potential has very little effect on that established by the potassium and chloride ions, which pass through more readily.

## Neural excitation

If an electric current passes through the excitable membrane, it can set off a nerve impulse if its intensity is above a certain value, called the threshold of excitation. With the closing of a current above this threshold the excitation always begins at the negative electrode.

The negative electrode or cathode reduces the positive charge in the external fluid and thus reduces the resting potential. A reduction in the membrane potential, called depolarization, results in an immediate outflow of potassium ions. But this depolarization has the supplementary effect of increasing the permeability of the membrane to sodium ions. The sodium concentration effect, which was previously of little importance because of the impermeability of the membrane to the sodium ions, now becomes increasingly important.

The entry of sodium ions increases and can reach or exceed the rate of outgoing of potassium ions. It is at this moment that the nerve impulse begins. As the influx of sodium ions exceeds the outgoing of potassium, positive charges are transferred towards the interior of the fibre and reduce the negative charge of the axoplasm. This depolarization, added to that caused by the action of the negative electrode, increases still more the permeability of the membrane to sodium. The entry of sodium ions at a slightly greater rate than the outgoing of potassium thus sets off an avalanche effect, in which the entry of sodium becomes so rapid that at the highest point of the nerve impulse there is a diffusion potential for sodium across the membrane of about 50 mV, the interior now being positive with respect to the exterior (fig. 2).

This comparison with an avalanche is very appropriate for the movement of the sodium ions. It can be demonstrated that the transfer of sodium ions across the membrane is very likely possible only by the combination of these ions with certain constituents of the membrane itself. This combination can occur only during the resting state while the exterior of the membrane is positively charged. Any depolarization of the membrane allows this combination to pass towards the interior of the fibre and to decompose, liberating the sodium. The current of sodium passing through the membrane, which may even be polarized in time, the more so since the depolarized membrane, which may even be polarized in the opposite sense during the sodium influx, changes in structure and also becomes more permeable to potassium. The influence of the current on the sodium ions disappears, while that due to potassium ions increases. The potential thus goes back to its original value, depending on the potassium and chloride concentration piles (fig. 3). What we call the nerve impulse is thus a rapid change in the membrane potential which occurs whenever the threshold of depolarization is reached. It always follows the same course in time, which can be shown diagrammatically as a triangle (fig. 3). The impulse, which is characterized by a series of changes in permeability and ionic currents, is entirely automatic and independent of the power of the electrical stimulus, provided always that this is above the threshold value.

The phenomenon of the rapid restoration of the 'resting' state after the initial avalanche of sodium ions is thus due partly to the temporary nature of the increased permeability to sodium and partly to the delayed increase of the permeability to potassium. This mechanism of excitation would fail after some time if the sodium which comes into the fibre at each impulse did not go out again, and if the potassium lost by the axoplasm at the same time was not restored to the interior. Recent researches, using radio-isotopes, have shown that as long as the cell is alive potassium ions are accumulated in the axoplasm, while sodium is continually removed from the cell owing to the cellular metabolism in which certain energy-rich substances are decomposed into simpler ones in the presence of oxygen. This ionic transfer, which takes place against the concentration gradient with the aid of metabolic energy, is known as 'active transport' of ions, or 'the sodium (or potassium) pump'. Its importance has only recently been realized; it is a fundamental principle of life for all cells.[2] Owing to this, the excitable cells, throughout their existence, keep an ionic concentration in their interior different from that outside, and this is the basis of all observed electrical phenomena. In the absence of oxygen and also in the presence of certain metabolic poisons, this inequality of distribution disappears.

## *The propagation of the impulse*

Once the principle of the origin of the impulse is known, the explanation of its propagation is simple. Fig. 4*a* shows a small area of an excitable membrane which has been stimulated by a cathode. The state of excitation will not be limited to a single point, for the difference in potential produced by the impulse will initiate the transmission of an electric current towards those parts of the membrane which are still in a state of rest (fig. 4*b*). It will be seen that this current is the same as that which we observe under the electrode of excitation. The depolarization which results will in turn activate the neighbouring part of the membrane and the state of excitation will spread to the left and right from the source of the impulse. If the nerve cell is the source, the excitation runs towards the periphery, is centrifugal, and is called an efferent impulse. If it starts at the periphery, for example, in the skin, and runs centripetally, it is called an afferent impulse. Physiological efferent impulses are generally destined to reach muscles or glands, to set in action either movement or secretion. Afferent impulses, on the other hand, often set off reflex phenomena in the efferent paths.

The fact that each part of the membrane

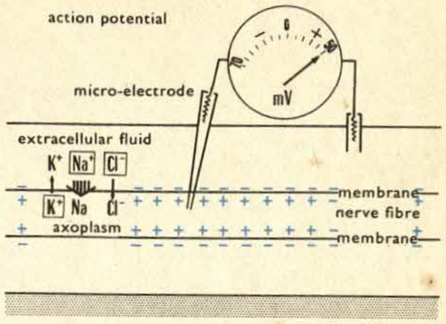


*Fig. 2. The situation which exists when the action potential is maximum. The very great increase in permeability of the membrane for sodium ions is the cause of the reversal of the electrical charge of the membrane.*

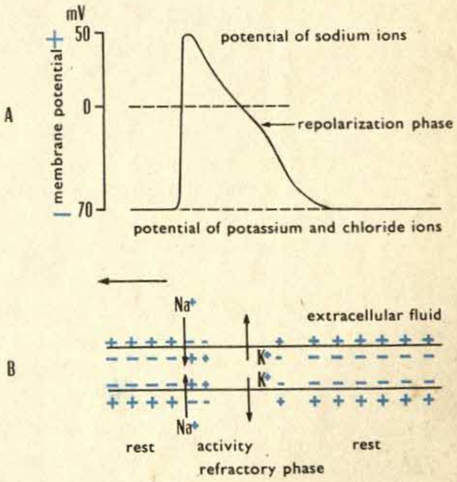


*Fig. 3. A. Action potential of the excitable membrane (duration, 0·001 sec.). B. Diagrammatic section of a nerve fibre conducting an impulse in the direction of the arrows. During the activity the fibre cannot be excited further and is relatively refractory during the repolarization phase.*

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(1) Axoplasm: *cytoplasm which is contained inside the membrane of a nerve fibre.*

(2) *See the chapter, 'Cellular Exchanges', page 41.*

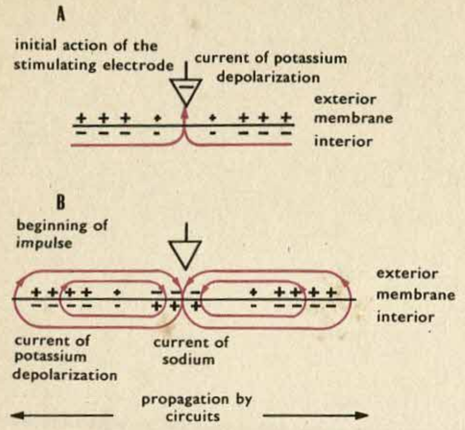
A
initial action of the stimulating electrode
current of potassium depolarization
exterior
membrane
interior
B
beginning of impulse
exterior
membrane
interior
current of potassium depolarization
current of sodium
propagation by circuits

*Fig. 4. A. The path of the lines of the current through the membrane at the beginning of electrical stimulation. B. The circuits which are formed after the start of the impulse which displace the situation shown in A towards the right and left. The impulse is thus propagated.*

successively undergoes the same phenomena of activation makes it clear why the impulse is transmitted along the whole length of a nerve fibre without losing any of its strength. The transmission is comparable to that along a fuse which contains a thin filling of gunpowder. Once the fuse is lighted, the fire is transmitted along the entire length without changing its intensity, since this depends on the amount of combustible material per unit length. The limited quantity of sodium which can be rapidly transferred to the interior of the cell, following the increase in permeability, determines the strength of the impulse. Once this transfer has taken place, no fresh excitation can be started until after a new reserve of sodium ions capable of passing the membrane has been restored. This chemical process takes a certain time, during which the membrane is inexcitable or refractory. This is why an impulse propagated in one direction leaves behind it a refractory area of membrane, so that it can never come back again. On the other hand, two impulses going in opposite directions disappear when they meet, for they cannot pass each other.

The speed of propagation of an impulse is not that of an electric current. The more powerful the current which passes through the electrical circuit, the more intense will be the activity at the surface membrane. If the fibre is of small diameter, the longitudinal resistance of the axoplasm will be high and the propagation will be slowed down, for the transfer of the quantity of electricity necessary to change the charge on the membrane will last for a long time. On the other hand, in a fibre of large diameter the speed of conduction will be higher, for the charging of the membrane will be swiftly brought to an end, owing to the reduced resistance of the axoplasm. It should be noted that the resistance varies with the area of the transverse section, ie, with the square of the radius, while the capacity varies with the length of the circumference, ie, with the radius itself. A variation in diameter must thus influence the speed of propagation of the impulse.

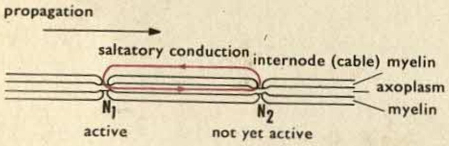

*Fig. 5. Propagation of the impulse by jumps (saltatory conduction) in a myelinated fibre. $N_1$, $N_2$, nodes of Ranvier. The impulse has reached $N_1$ and, by the conductive properties of the internodal space, is propagated towards $N_2$.*

## The special properties of myelinated fibres

To make things simpler, we have until now spoken as if all the nerve fibres in the human body are constructed in the same way. But in fact there are two main morphological classes. They are the non-myelinated fibres which are covered entirely with a membranous sheath, and the myelinated fibres which have along their length an insulating sheath of myelin. Ranvier was the first to notice, however, that this sheath is interrupted every 1 or 2 mm. At these points the fibre is greatly narrowed. These points are known after their discoverer as the 'nodes of Ranvier'. Recent researches have shown that the myelinated fibre possesses an excitable membrane only at these nodes.

In view of this latter property, the problem of the propagation of the impulse can be seen in this case to present a somewhat different aspect. As in the example we have already given, electrical circuits are formed, but, owing to the insulating sheath of myelin, they can cross the membrane only at the next node of Ranvier (fig. 5). Owing to this peculiarity of construction, the capacity of the membrane is now very small. Very feeble currents will discharge it enough to allow it to reach the threshold of excitation. The impulse, instead of passing uninterruptedly as a wave along the fibre, now jumps from one node to the next, the part of the fibre in between playing only a passive role as a conducting cable. This transmission of the impulse by jumps from node to node is known as saltatory conduction and it allows the organism to make great savings in energy. Fibres of small diameter can now conduct at great speed. The passage of ions through the membrane at the moment of impulse is limited to the nodes, and so the energy needed to return the ions to their original place, after the passage of the impulse, is greatly reduced.

## Saltatory conduction and the transmission of information

Animals which possess myelinated nerve fibres, and particularly man, can transmit a large amount of information and orders very rapidly throughout a complex network of nerve connections. A similar organism possessing only non-myelinated fibres having the same speed of conduction would become an enormous mass of nervous tissue, which by its bulk and weight would encumber movements and would use up most of the oxygen collected in the lungs through respiration. It seems certain that the great diversity of reactions, and the great speed with which they happen in the higher animals, are direct consequences of the appearance of saltatory conduction during the course of evolution.

# Propagation of the nerve impulse

### Bernard KATZ

*The purpose of this chapter is to consider what happens at 'synapses', the points of contact between one nerve cell and the next, or between nerve and muscle fibre. There is no sign of cytoplasmic continuity between the different cell units. Electron microscopic evidence shows that the membranes of the synapsing cells are arranged in close proximity, though in general they do not seem to fuse or to come into intimate contact.*

## Electrical and chemical transmission

There are, in principle, two basically different modes of synaptic transmission, electrical and chemical. *Electrical* transmission implies that, in spite of apparent morphological complexities, an effective local-circuit connection exists which allows sufficient current to pass from one cell to the next to restimulate it. In other words, the transmission is one continuous process without any essential change at the synapse. There must, of course, be *some* difference; for all synapses have the property of functioning only in one direction, unlike nerve fibres which can conduct impulses with equal facility in either direction, despite the fact that in normal life, because of their terminal synaptic connections, they are used for one-way traffic only.

*Chemical* transmission implies the intervention of an entirely different process specific for the synaptic area. It presupposes that the ordinary cable-connection is interrupted at the contact point between the cells and replaced by the agency of a chemical mediator. A specific chemical stimulant which is synthesized and stored inside the nerve terminal is liberated by the nerve impulse. When the substance is released, it attaches itself to special receptor molecules in the surface of the contacting post-synaptic (or effector) cell. This chemical combination leads to a membrane change which gives rise to a local depolarization of the effector cell. When the depolarization exceeds the threshold level, a new action potential is set up which then travels along the cell in the manner previously described. Thus, interposed between two separate waves of propagated electrical activity, there is a secretion of a specific substance from one cell, and a chemoreceptor reaction in the next cell.

It is not possible to predict, without thorough experimental examination, which of these two modes of transmission corresponds to a particular type of synapse. Various attempts have been made to generalize by drawing analogies from the few cases which have been explored; and in recent years the view has become prevalent that transmission is likely to be chemical at all synapses, but that various substances are being employed in different cases, and only a few of them, like acetycholine and noradrenaline, have so far been identified. This view, however, seems a little too sweeping, and the discussion is begun, therefore, by quoting an example of electrical transmission which has been brought to light by the work of Furshpan and Potter. This may well be an exception to the rule, but it provides a definite warning against too much generalization in this field.

Furshpan and Potter used a 'giant' synapse in an abdominal ganglion of the crayfish cord. There is a contact point between a very large nerve fibre which runs through the central nervous system of the crayfish and a somewhat smaller motor axon which emerges from the cord to supply the flexor muscles of the 'tail'. Furshpan and Potter were able to show that the membrane contact of this special synapse acts as a good electrical rectifier, allowing current to pass relatively easily from the pre-synaptic to the post-synaptic cell, but not in the reverse direction. In other words, at this particular synapse, an adequate cable connection exists between the interior of the two cells, in the normal orthodromic[1] direction of impulse travel alone.

Thus, at the giant synapse of the crayfish, a case is found—so far, the only known example—of electrical transmission, in which the action current generated by the arrival of an impulse on the pre-synaptic cell is passed on

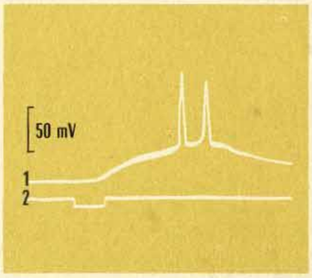

*Fig. 1. By means of micro-electrodes (slowly ascending part of curve 1) local depolarization of the motor plate of a single muscle fibre is shown. On the surface of this a very small quantity of acetylcholine is made to appear (ionophoresis) ie, transfer by means of an electric current (during the time indicated by the dip on line 2). When local depolarization has reached a certain value, two successive action potentials appear (the short high peaks of 1) which travel along the muscle fibre and cause its contraction.*

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(1) Orthodromic *(or* normodromic*) describes the direction of a nerve impulse when the path it takes along the nerve fibre is the one it usually takes. When a nerve fibre is artificially stimulated at any given point, the nerve impulse goes in two directions and is thus orthodromic on one side and antidromic on the other.*

*(2) The most direct way of showing chemical transfer by means of nerve impulses would be to establish that a nerve stimulus results in the emission of a chemical substance which enters the blood circulation, and that stimulation of a distant effector cell similarly inhibits or excites. This demonstration is*

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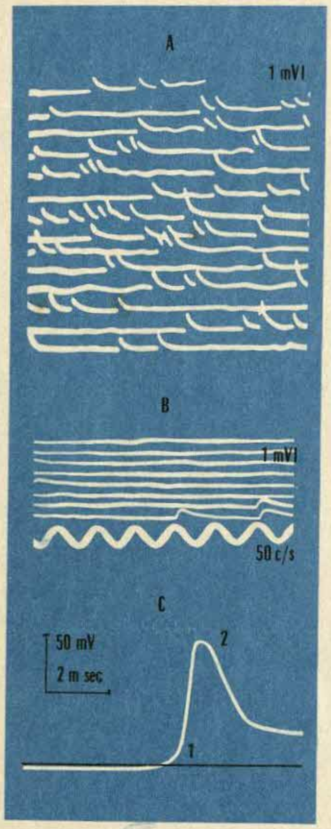


*Fig. 2. A: small spontaneous plate potentials registered by micro-electrodes at a neuro-muscular junction. B: a striking reduction of the frequency of emission of these miniature potentials when the fibre is placed in an abnormal medium, poor in calcium ions and rich in magnesium ions. The voltage of these miniature potentials is about 1 mV. C: the effect of a nerve impulse. An ample motor plate potential occurs (1) on which is grafted the action potential of the muscle fibre (2). The amplitude of (1) is about 20 mV and that of (2) is 70 mV.*

without discernible delay and can directly depolarize and thereby excite the post-synaptic fibre.

If an entirely different case is taken—namely, the skeletal neuromuscular junction—there is found here one of the few examples of a synapse where chemical transmission[2] has been firmly established. It was shown by Dale and his colleagues that a specific cholinester, almost certainly identical with acetylcholine, is released from the active motor nerve endings. This substance is a very potent local stimulant and, provided it is applied rapidly to the junctional end-plate region of a muscle fibre, it causes a local depolarization of the cell membrane and sets up propagated impulses and contraction in the fibre. The chemical effect is localized in the synaptic area of the muscle surface; it is in this region exclusively that a number of chemical blocking agents, like curare, show a specific activity (apparently by a competitive attachment to the acetylcholine receptors). By histochemical methods, a high local concentration of a specific enzyme, acetylcholinesterase, has been found at the same point; the apparent purpose is to hydrolyze the transmitter substance within a very short time after it has exerted its action. Electrical studies have shown that there is an irreducible delay of 0·5 to 1 millisecond between the arriving nerve impulse and the start of the so-called end-plate potential (which is the local depolarization in the muscle fibre produced by the transmitter substance). There is no cable transfer of electric current, of either polarity, directly from the nerve axon to the muscle fibre. When potential changes are imposed on the terminal portion of the motor nerve, these changes do not spread beyond the nerve terminal, but can be shown to increase the rate at which acetylcholine is being released from the nerve endings and so, indirectly, to influence the membrane potential of the muscle fibre.[3]

The principal features and problems inherent in chemical transmission in general may be considered briefly. There are two main steps interposed between the arrival of a presynaptic and the departure of a post-synaptic impulse: (i) the process by which the arriving impulse releases the transmitter substance, from its storage place inside the terminal, into the narrow cleft between the contacting cells—this is a special case of what has been called 'neuro-secretion'; (ii) the process by which the transmitter substance becomes attached to specific molecules in the post-synaptic cell surface and causes its electric membrane properties to change—this is a special example of *chemoreceptor* action.

## *Excitatory and inhibitory chemoreceptor action*

Let us consider the second step, ie, the chemoreceptive mechanism. How do transmitter substances alter the membrane potential? In general, the primary action leads to the opening of some ionic permeability channel in the membrane. Depending upon the size or specificity of this ionic channel, the membrane potential either tends to fall to a low level, well beyond the firing threshold of an impulse, or it may become stabilized in the vicinity of the resting level or even tend to rise somewhat (hyperpolarization). In the first case, excitation ensues; in the second case, there is an inhibitory action. But it may be noted that, underlying all these changes, there is a common primary effect—namely, an increase of some ionic conductance.

For example, at the motor end-plate there is evidence that acetylcholine causes the membrane permeability to increase, simultaneously, to certain monovalent cations (eg, sodium, potassium, ammonium) and possibly opens up an indiscriminate aqueous channel to all small ions on either side of the membrane. The result is a depolarization which has a 'zero point' at about 10 to 20 mV, negative inside, which corresponds to the level of a free-diffusion or liquid-junction potential between cytoplasm and external fluid. The effect is to short-circuit and depolarize the surrounding muscle membrane beyond the level at which a new impulse arises. This impulse then travels rapidly along the whole length of the muscle fibre. The methods by which these conclusions were reached have been described elsewhere. Briefly, they consist of measuring the current/voltage relation across the end-plate membrane, and observing the particular level of the membrane potential at which the electromotive effects of ACh are reversed, with normal as well as with altered composition of the ionic environment.

While ACh has a depolarizing and excitatory effect at the end-plate, it produces the opposite action, ie, hyperpolarization or stabilization of the resting potential, in the regions of the heart muscle on to which it is released by impulses in the vagus nerve. Here also, the basic effect is an increase of ionic conductance, but the channel which is being opened is restricted to potassium, and does not include sodium.

Somewhat similar changes appear to be associated with the excitatory and inhibitory synapses in the motor neurons of the spinal cord. At these junctions, the transmitter substances are unknown.

Although the transmitter effects are fairly well understood in terms of ionic conductance changes, and the subsequent steps leading to excitation or inhibition present no special problem, the molecular mechanism by which the chemical attachment, eg, of acetylcholine, to the receptive sites of the membrane alters its permeability, is still far from being understood.

### *Quantal nature of acetylcholine release*

An interesting feature which has emerged during a detailed study of the vertebrate nerve-muscle junction is that the release of ACh from the motor nerve terminals occurs in discrete groups or quanta, each containing a large number of molecules. Even in the absence of a nerve impulse, such groups are released 'spontaneously' at infrequent random intervals (fig. 2). The arrival of an impulse at a cell junction apparently causes a few hundred events to be synchronized within a fraction of a millisecond, instead of their going on at a leisurely average rate of about 1/sec.

The evidence for this state of affairs was obtained soon after it became possible to apply intracellular recording electrodes to the motor end-plate. If a recording electrode is inserted into a resting muscle fibre well away from its junctional region, a steady resting potential of about 90 mV, negative inside, is observed. But as the end-plate is approached with the recording probe, a characteristic form of spontaneous activity shows up, consisting of an intermittent random discharge of minute potential changes of standard size and time course. The discharges resemble in many respects the end-plate potential (e.p.p.) —ie, the immediate depolarization of the end-plate produced after the arrival of a nerve impulse—but they differ from it in their then much smaller size (about 1 per cent) and spontaneous random occurrence. Fatt and I called these currents 'miniature end-plate potentials'. They resemble the e.p.p. in time course, restricted localization to the innervated region of the muscle fibre, and in their pharmacological reactions. The potentials are reduced in size by curare, and the amplitude and duration increase when the local hydrolysis of ACh is prevented by a potent anti-esterase. In both respects, the miniature potential behaves exactly like the depolarizations produced by an applied dose of ACh, and we believe, therefore, that the spontaneous discharges arise from local random impacts of ACh on to the end-plate receptors. The source of these impacts is evidently a spontaneous release or leakage of ACh from the motor nerve terminal where the substance is stored, for the miniature potentials vanish in the course of experimental nerve degeneration, at a time when neuromuscular transmission fails.

The effects of single molecular impacts of ACh are far below the resolving power of our recording equipment, and the discrete miniature e.p.p., with its standard size and brief time course, must be due to a synchronous mass of ACh molecules, possibly thousands of them, discharged in the immediate vicinity of the end-plate receptor.

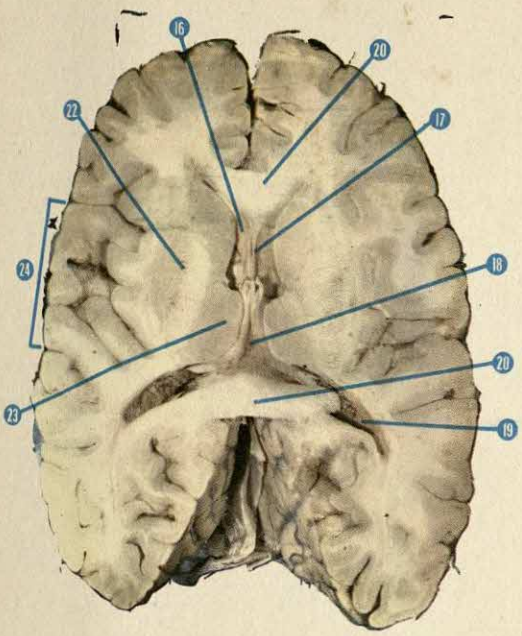
Transmission is brought about by a summation of many of these quantal units of activity. The size of the unit mass of ACh which is delivered from the nerve endings, spontaneously or in response to an impulse, is relatively constant at all cell junctions and apparently quite unaffected by the many changes which may be imposed on the system in the course of an experiment. On the other hand, the probability of release of any one mass in a given time-interval—ie, the frequency of the miniature potentials—can be altered by several orders of magnitude, eg, by electrically depolarizing the nerve ending with a steady current, or by changing the chemical composition of the environment. The action of the nerve impulse itself can be described as causing a momentary enormous increase in the frequency of the miniature potentials (by a factor of nearly $10^6$, provided a high Ca/Mg ratio exists in the surrounding medium).

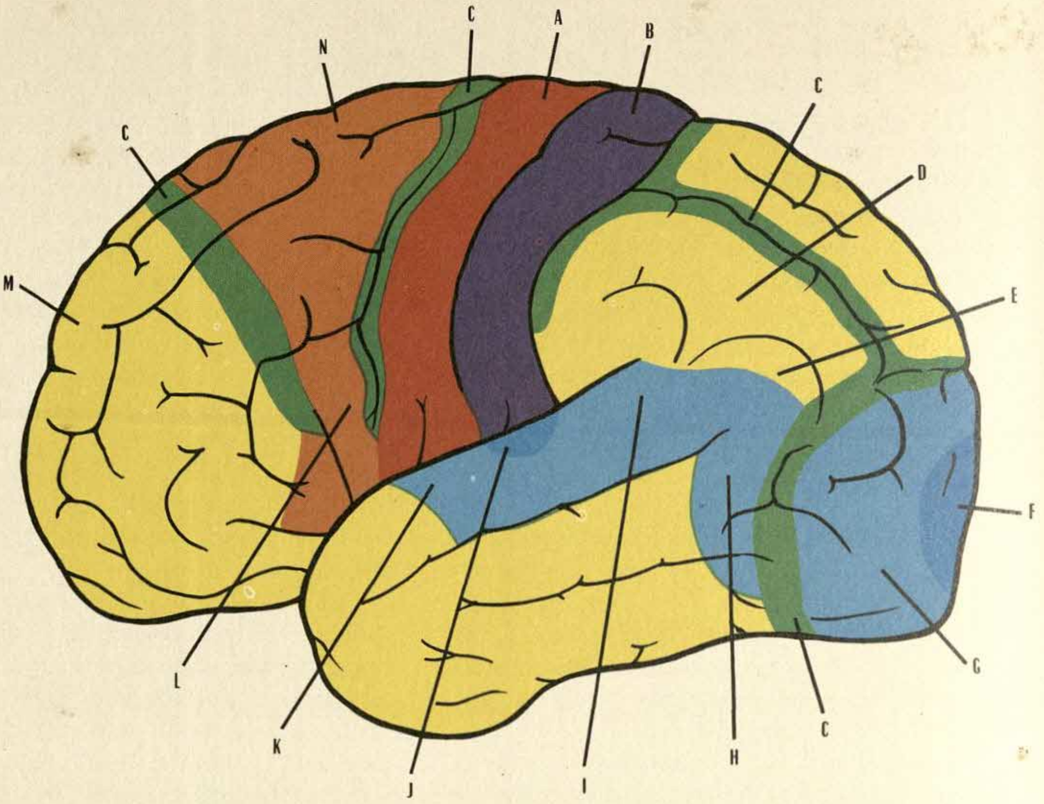
The basis of this multimolecular quantum of ACh release is not yet known; an attractive suggestion is that the transmitter substance is stored, within the nerve endings, in minute intracellular corpuscles from which it is discharged at the surface in an all-or-none manner. Electron micrographs have revealed a mass of fairly densely packed so-called vesicles inside the nerve terminals, and it is conceivable that these are the intracellular receptacles in which ACh is stored prior to its release. It is possible to imagine mechanisms by which a collision between such particles and certain critical sites in the nerve membrane could bring about sudden liberation of the vesicular contents straight into the synaptic cleft. But more work is needed to put these ideas on a firm experimental basis.

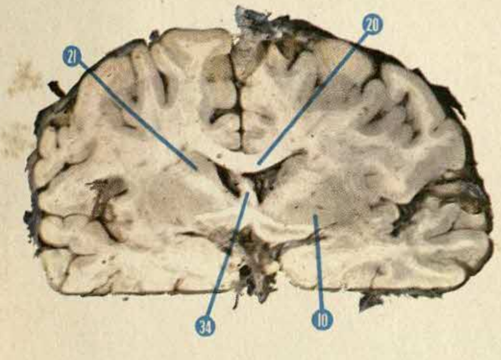
**Continued from previous page**

*possible in some cases, as in the classic experiment in which Otto Loewi proved that acetylcholine carries impulses inhibiting heart-beat. This kind of direct experiment is not, however, often practicable.*

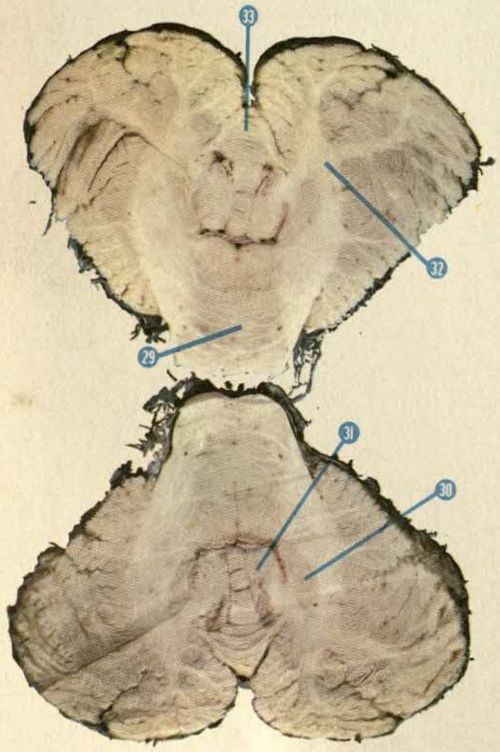
(3) *The disproportion that exists between the quantity of acetylcholine (ACh) required to stimulate a muscle artificially and the minute quantities given out by the nerve endings in the perfusion fluid has been pointed out by opponents of the chemical transfer theory. By means of micro-ionophoresis, however, it has recently been possible to reduce considerably the effective quantity, and it has been shown that* $10^{-16}$*g of ACh is sufficient to cause effective depolarization of the upper myofibre at the critical level. Other encouraging results have been obtained with electrophoresis. This exploratory technique has confirmed that chemoreceptors are strictly limited to the neuro-muscular junction and within it. By displacing the extremity of the pipette a few microns, the effect of a given amount is markedly reduced. It has also become possible to introduce the pipette into the cell, which allows the acetylcholine to be placed in contact with the inside of the terminal plate. Trials with ACh, carbamylcholine (which has similar effects but is not destroyed by cholinesterase) and with an inhibiting substance such as curarine, have been conclusive. It appears that the process of fixation of the chemical substance to the receptor molecules occurs on the external face of the plate which is turned towards the nerve endings which diffuse normally.*

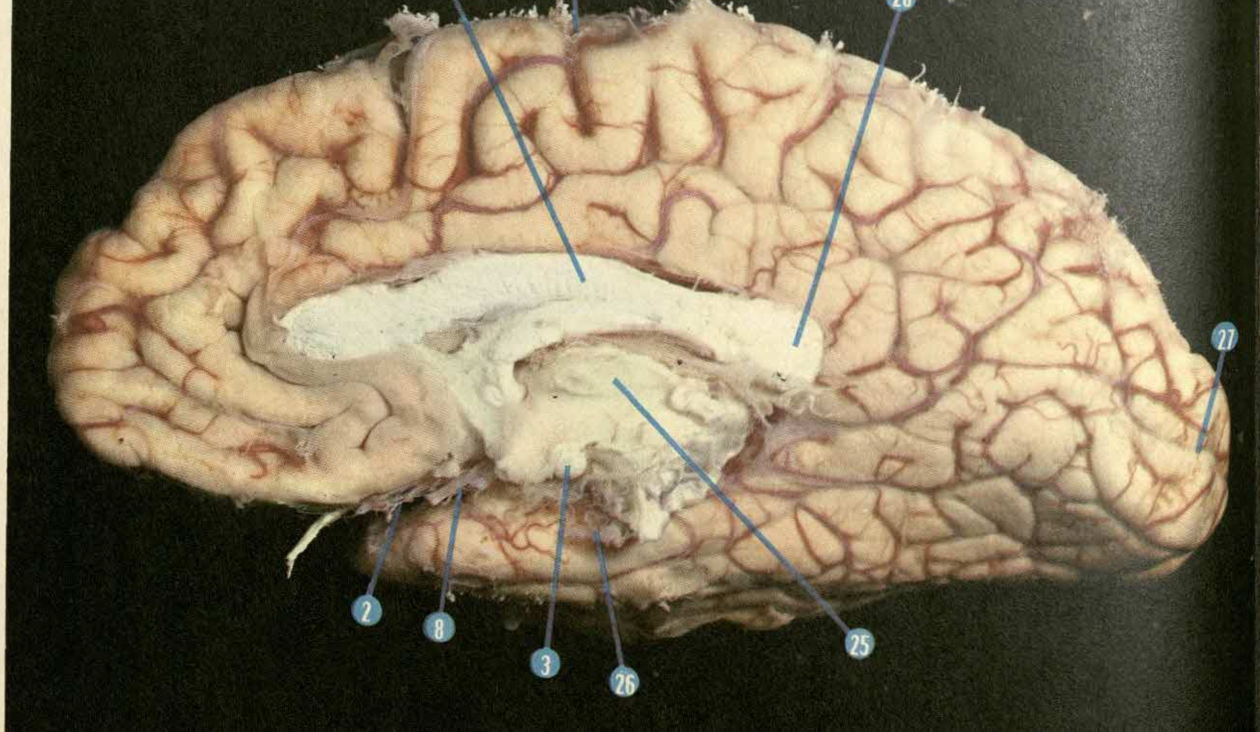






*Experiments on animals and human neuropathology have enabled the sites corresponding to different motor and sensory functions to be localized on the surface of the cerebral hemispheres. The diagram represents the lateral surface of the left hemisphere. The chief cerebral localizations are shown as differently coloured areas. A: area of voluntary motor activity; B: area of projection of cutaneous sensitivity; C: suppressive areas; D and E: association areas (E may be linked with handwriting); F: portion of visuosensory area; G: peristriate; H: may be linked with reading; I: may be linked with understanding the spoken word; J: primary area of hearing; K: auditopsychic area; L: motor centre of speech; M: pre-frontal lobes; N: pre-motor area. The other illustrations on this page are actual views of different parts of the human brain and the brain-stem. Above left, horizontal section of the brain taken through its greatest dimensions; centre, frontal section of the brain taken through the basal nuclei; below right, view of the superior surface of the right cerebral hemisphere; below left, section of the brain-stem taken through the* pons Varolii *and the cerebellum, where the 'tree of life' can be clearly seen. 2. lateral sulcus; 3. mamillary body; 8. optic chiasma; 10. lenticular nucleus; 14. central sulcus; 16. lateral ventricle; 17. septum lucidum; 18. third ventricle; 20. corpus callosum; 21. caudate nucleus; 22. putamen; 23. thalamus and optic radiation; 24. insula; 25. optic thalamus; 27. calcarine fissure; 28. splenium of the corpus callosum; 29. superior cerebellar peduncle; 32. cerebellar white matter; 33. median vermis. (Photos Lod. The diagram is based on that of Frank H. Netter in* The Nervous System, *published by Ciba).*





# Cerebral localization

### Paul LAGET

*The authors of antiquity, right up to the Renaissance, indulged in many speculations about the localization of consciousness. Some suggested that the cerebral ventricles are the seat of the 'soul'; others made diagrams on which were marked the supposed localization of the various mental faculties in different parts of the brain. The neurologists of the seventeenth century, such as Vieussens and Willis, were the first to establish experimentally that in fact consciousness depends on the cerebral substance and is not located in the ventricles. They also distinguished between the functions of the cerebrum and the cerebellum as to their role in motivity, the first having control over voluntary, and the second over involuntary, motivity.*

We had to wait, however, until the nineteenth century and the progress in medical and biological science which occurred then, in order to have a more precise idea of the fine structure and the role of the different parts of the cerebral hemispheres, in particular of their covering of grey matter, made up of millions of neurones and of some of their prolongations, to which we give the name 'cerebral cortex'.

Thanks to the closely associated techniques of anatomy, histology, neurophysiology and neurosurgery, we now know a great deal about the structure and function of the cortex. In particular, it has been possible to establish for man and for animals 'cortical fields' of which the structure differs from one to another. We also know that some control the functioning of the voluntary motivity of this or that part of the body, whilst others are the point of arrival and termination of all the great sensory pathways and of those conveying the various types of cutaneous sensitivity.[1]

## *The structure of the cortex*

Let us first of all briefly recall some data on the histological structure of the cortex. Its actual thickness, which rarely exceeds 1 mm, varies from one region to another. Thus it is thin on the interhemispherical face of the occipital lobe around that furrow called the 'Calcarine fissure', where it is only half a millimetre thick, whereas in the parietal and frontal lobes it is thicker. Looking at it in detail, one finds innumerable neurones of reception, of association,[2] those that are the starting point of the motor pathways, and others arranged in layers superimposed on one another.[3] Their prolongations, particularly the dendrites, and innumerable non-medullated axons, form synapses with the cell bodies in the various layers. We must also remember that those most important elements in the cortex, the neurones, are in fact embedded in a felt-like network of supporting cells, the neuroglia, whose function is as yet little understood.

The arrangement of the cell bodies and their prolongations in the cortex appear as an extremely complex interweaving, but some histologists, notably Cajal and Lorente de No, have succeeded in identifying certain types of structural organization which are frequently repeated. One of their main common characters is without doubt the multiplicity of interneuronal connections, which put each neurone more or less in contact with all parts of the cortex. The size and types of the cellular elements which make up the different cortical

(1) Cutaneous sensitivity: *this covers the various kinds of sensation to which our skins are sensitive, such as touch, heat, cold, and pain. For each type of sensation there are sensitive nerve endings of a specialized character, and special nerve tracts to the brain.*

(2) Associative neurones: *the term used for certain neurones (also called interneurones) which draw together numerous synaptic connections with other neurones that do not belong to the main motor or sensory pathways.*

layers and their relative proportions vary from one place to another. Certain histologists, among them Vogt, Brodman, von Bonin and Bailey, have thus been able to prepare maps of cerebral 'areas' whose limits rest upon structural differences. These different areas, of which the boundaries often, though not always, coincide with various anatomical landmarks (furrows, fissures, etc) also correspond frequently to differences in physiological function. Thus the areas containing the giant pyramidal cells of Betz[4] are characteristic of area 4, in which the main voluntary motor tracts originate. The areas which contain hardly any pyramidal cells but innumerable smaller cells called 'granular cells'[5] are characteristic of the reception and termination zones of the main sensory pathways (conscious cutaneous sensitivity for areas 1 and 3, visual for area 17, auditory for area 41).

## *Cortical representations in the cerebral areas*

The different cerebral areas which we have indicated not only possess very different functions, but also reproduce in miniature a projection of the parts of the body which they control. Thus in area 4, on the ascending frontal convolution (called the primary motor area), an electrical stimulation of a certain point will produce a movement of the thumb or the lowering of the foot, these movements always occurring in the muscles on the opposite side of the body from the hemisphere which is being stimulated.

Thus it is possible, by stimulating the brain of human beings during the course of neurosurgical operations, or by stimulating those of the higher apes and other mammals, to obtain maps of the surface of the cerebral hemispheres corresponding to the point of origin of the nerves leading to the different parts of the body. The same applies if one stimulates the sensory cortex. A conscious individual then describes sensations identical with those which would be produced by the stimulation of certain regions of the body, or of the sense receptors. For example, if one applies an electrical stimulus[6] to the cortical area corresponding to the visual projections, the patient will describe sensations such as flashes of light, luminous patches, or coloured shapes. If the electrical stimulation is applied to the area corresponding to the projections of the cutaneous sensitivity of the left foot, then the patient will describe a sensation of touch or tickling in that foot.

The neurophysiologists have thus mapped out the cortical projections of sensation and the cortical motor areas, but such a map has also large areas which are blank. What do these areas represent and what happens if they are stimulated? They can be divided into four groups:

1. Those which, when stimulated, cause either motor activity or some sensation, but this time much more diffuse and poorly localized. They may also affect both sides of the body. These are secondary or supplementary motor or sensory areas. Their functional connections and their role are as yet little understood.

2. Areas which are concerned with language. Naturally, these have been found only in man. Stimulation of these areas never gives rise to utterance, but, on the contrary, to the interruption of whatever the subject is saying at the time or to the impossibility of his finding the name of an object or the word he needs to continue the conversation.

3. Areas the stimulation of which give rise to actual hallucinations of a visual or auditory character. These may be comparable with the recalling of actual scenes, and with the evocation of auditory, visual, and, to a certain extent, affective memories.

4. Finally, the whole of what is called the prefrontal cortex is a silent area, ie, no response is obtained when it is stimulated. Thus the role played by these prefrontal areas cannot be determined by the procedure of stimulation. It is through the operations performed by neurosurgeons that we have finally become aware that they are associated with the structure of the personality itself and are used apparently in the highest mental processes.

The cerebral cortex of mammals, including man, has many areas the stimulation of which produces no conscious motor or sensory effects but those of the involuntary or autonomic nervous system; ie, they may produce changes in vasomotor regulation, in the rhythm of respiration, in the motivity of the digestive tract, etc. One could thus speak of a 'visceral brain' in juxtaposition with the 'motor brain' and the 'sensory brain'.

However, in spite of the amount we do know about it, the working of the cortex which covers the cerebral hemispheres still presents many problems. The relations linking the billions of cortical cells and the important psychological functions such as memory, learning, and will, are still very obscure and their elucidation will take the efforts of many patient research workers for a long time yet.

(3) Cortical layers: *the six cortical layers are distinguished from each other by the shape, size, and abundance of the nerve cells which form them, as well as by their thickness.*

(4) Betz cells: *cells of large size (50 to 70 microns in diameter) and pyramidal form which are found in the internal pyramidal cortical layer. The apical dendrite, arising from the top of the cell, runs up into the external cortical layer where it splits into two horizontal branches which may be as much as 1 mm in length. The axon which comes out from the base of the cell becomes enveloped by a myelin layer as soon as it reaches the white matter.*

(5) Granular cells: *these are small cells (8 to 15 microns in diameter) of pyramidal or rounded shape and which have numerous dendrites. These are short and branching. The short axon that is not myelinated remains within the cortex.*

(6) Electrical stimulation of the cortex: *the electric currents used for this type of research are shocks of low voltage (0·1 to 2 volts) and of very weak intensity (about 1 milliamp) which last only a short time (0·5 to a few milliseconds) and can be of varying frequency, from ten to several hundred per second. The different physical characters of the stimulation, ie, the voltage, intensity, frequency, etc, must be kept strictly constant from one experiment to another, if comparable results are to be obtained.*

# Electrical activity of the brain

### Herbert H. JASPER

*The human brain exhibits ceaseless electrical activity from birth until death. Awake or asleep, in coma or under deep surgical anaesthesia, various forms of electrical activity continue as long as the brain is alive. Prolonged disappearance of the electrical activity of the brain is as sure a sign of death as is the silence of the electrocardiogram when the heart stops beating. But, of course, the electrical activity of the brain is far more complicated than that of the heart, even though both can be recorded from electrodes attached to the skin.*

The electrical activity of the human brain was first described by Professor Hans Berger of Jena, Germany, in a series of papers beginning in 1929.

Making use of patients with defects in their skulls, Berger first inserted needles through the scalp and through the small holes in the skull, to rest on the surface of the brain. These small metal needles acted as electrodes from which could be derived the very small electrical currents generated on the surface of the brain. It was necessary for these currents to be amplified and then connected to an oscillograph recorder of the type then used for electrocardiography.

Surprisingly, it was found that the electrical rhythms of the brain, recorded across the surface of the head, were remarkably simple in form despite the amazing complexity of the activity of the brain itself. In the normal adult subject resting quietly though awake, there seemed to be one principal rhythm characteristic of the brain which Berger called the *alpha rhythm.* This was a quasi-sinusoidal regular oscillation of variable amplitude, but it showed remarkably little variation in frequency in normal adult men. It was found to be between about 8 and 12 cycles per second.

A second rhythm described by Berger was of lower voltage and higher frequency, namely at about 18 to 25 cycles per second. This rhythm was called the *beta rhythm.*

It was soon found that it was not necessary to pierce the skull to record the EEG. With sufficient amplification, quite a faithful record of the major surface components of the electrical activity of the brain can be recorded from electrodes attached to the surface of the scalp with the skull intact. This opened up an entirely new field of study of the human brain, known as electroencephalography.

With the development of multi-channel ink-writing EEG machines, as shown in fig. 1, hundreds of laboratories have sprung up all over the world, and thousands of miles of EEG tracings or brain waves have been taken from human brains under almost every conceivable condition from birth to senility. The disturbances in brain wave patterns accompanying practically every known disease of the brain have been described; that is, when there were alterations, for some diseases or impaired functions of the brain do not produce significant alterations in the EEG.

## *The normal electroencephalogram*

At birth electrical brain wave patterns are slow, irregular, and quite amorphous. During the first few weeks of infancy some regular rhythmic waves begin to appear, especially over sensory-motor regions. Then gradually particular patterns of electrical activity appear during sleep, distinct from those seen when the infant is awake. From posterior head regions, the slow electrical rhythms become regular, with a frequency of 3–4 per second when the infant reaches about 3 months of age. Gradually this nascent alpha rhythm becomes more regular and increases in frequency, to come within the adult 8–12 c/sec range usually at 8 to 10 years of age. The beta rhythm at 18–25 c/sec, sometimes mixed with 8–10 c/sec waves, is characteristic of the central or sensory-motor regions.

Brain wave patterns, and their distribution

(1) Asynchronous activity: *during asynchronous activity the neurones function over a great interval of time. This term contrasts with that of synchronous activity, where a large number of neurones enter into action at the same moment and hence give out stronger electric signals.*

(2) Hypoglycaemia: *a fall in the level of blood glucose below the normal figure (1·33 g/pint).*

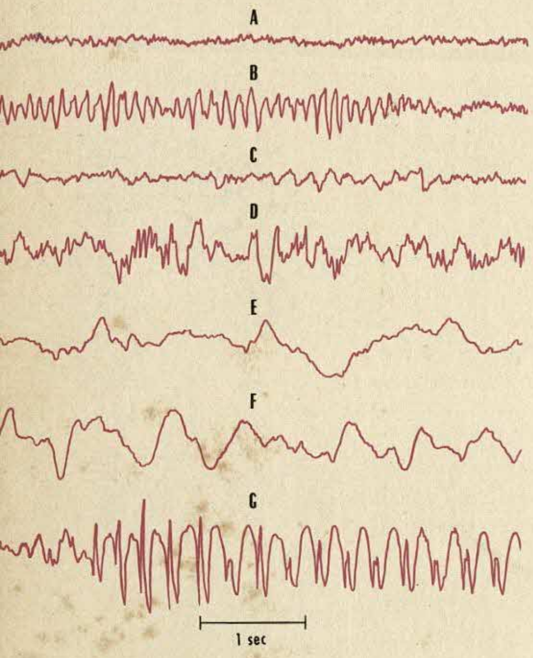


*Fig. 1. Characteristic curves corresponding to different states of consciousness: A: subject awake and attentive; B: subject resting; C: subject sleepy; D: light sleep; E: deep sleep; F: coma from encephalitic damage; G: 'petit mal', accompanied by a short loss of consciousness (1 mm = 10 μV).*

over the head, are quite constant under standard conditions in a given individual from day to day, after his brain has matured, but there are wide differences between one person and another. Some people, for example, hardly ever show any alpha rhythm from posterior head regions. Others have a high voltage continuous rhythm at 8 per second, while others may show a lower voltage, less continuous rhythm at 12 c/sec; and there are many other such differences.

Identical twins tend to have almost identical brain wave patterns, indicating a strong hereditary determinant. Some think that traits of personality may be shown by the EEG, but this has not been definitely proved. Neither are the brain waves related to intelligence; Einstein's EEG was not much different from that of an apprehensive taxi-driver, and even bore some resemblance to the electrical rhythms recorded by Adrian from the brain of a goldfish.

## *Relations of sleep and states of consciousness*

Despite the lack of relationship found between brain waves and many higher mental processes, the EEG is very sensitive to alterations in states of consciousness. Concentration of attention, emotional excitement, or a sudden startling noise, arrests or blocks the slow rhythms of the brain, leaving lower voltage asynchronous[1] rapid activity characteristic of alertness, heightened vigilance, or emotional excitement. Alpha waves appear most strongly when the eyes are closed and the mind is at rest, but they tend to disappear with the onset of drowsiness (see fig. 2).

In drowsiness, slow waves replace the alpha waves, and spindles of 14 c/sec waves (sleep spindles) replace the beta waves from the central regions of the head (fig. 1d). These too disappear in deeper sleep when large slow waves dominate the entire record from all parts of the head (fig. 1e). Characteristic changes then occur in response to sounds or other stimuli which do not waken a person, and we can tell when someone is dreaming by the changes in the sleeping brain wave patterns.

Important changes also occur when a person is knocked unconscious by a blow to the head, or when he is comatose following a brain lesion (such as a stroke), or through any other cause (such as diabetic coma). Slow waves predominate in the EEG in all such conditions (fig. 1f).

The electrical activity of the brain is very sensitive to alterations in brain metabolism, such as occur with low blood sugar, deficient oxygen in the respired air and deficient blood supply, or any other cause of interference in metabolism, such as thyroid deficiency. Usually, such factors, which decrease metabolic rate, cause a marked slowing of the brain wave frequencies, and if sufficiently severe, a complete disappearance of all electrical activity may occur. With complete arrest of cerebral circulation, for example, in a pilot suddenly subjected to high forces of acceleration, the brain waves may disappear within 8-12 seconds.

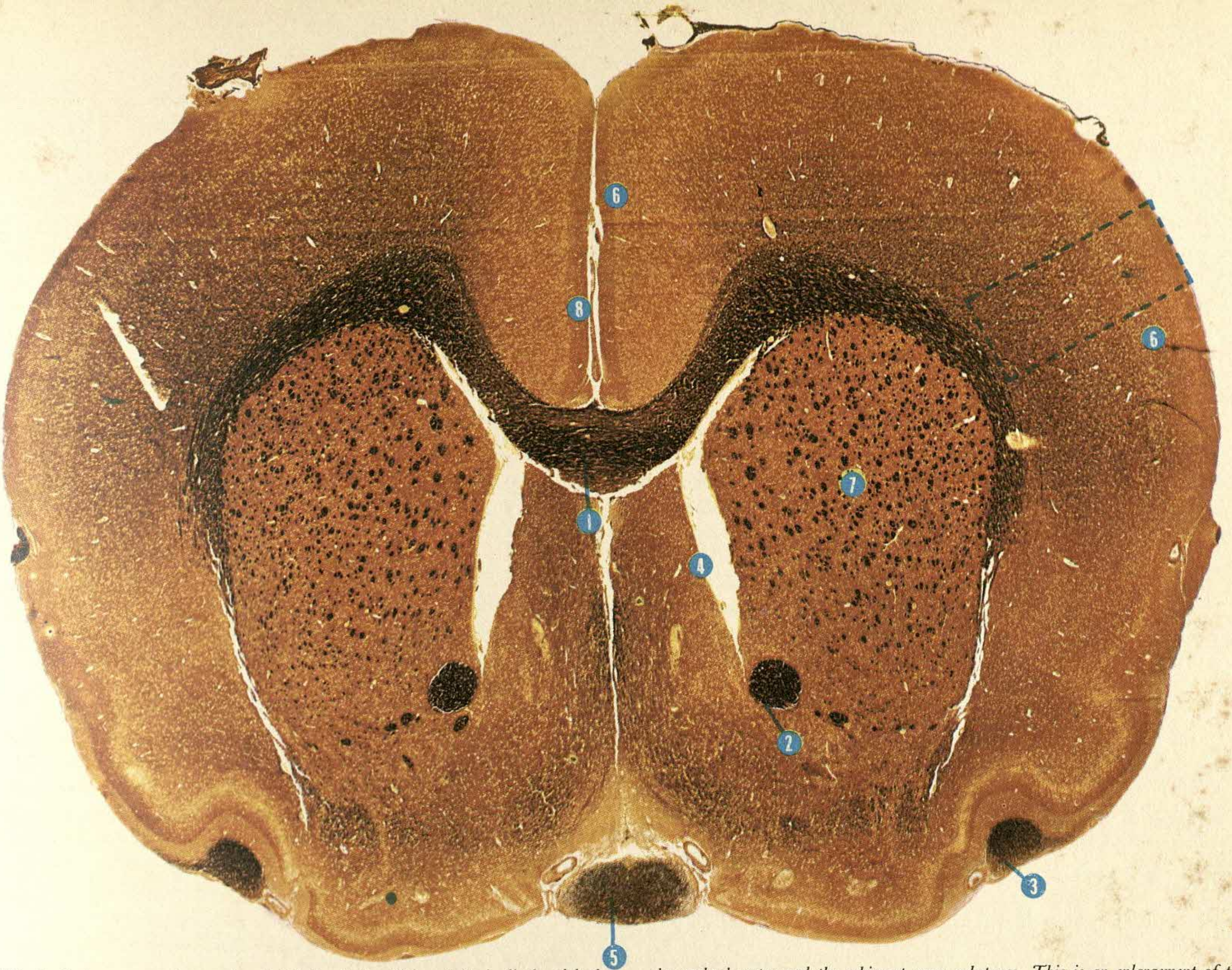
Anaesthetic agents cause rapid and marked changes in the brain waves which characterize the different levels of anaesthesia. An attempt has been made to use these changes to actuate a servo-mechanism attached to a power-driven syringe, to provide for automatic control of the level of anaesthesia by the patient's own brain waves. Although it is ingenious, most surgeons would prefer to keep an anaesthetist nearby, to be sure that the automatic instruments are working properly.

## *Conditioning and lesions*

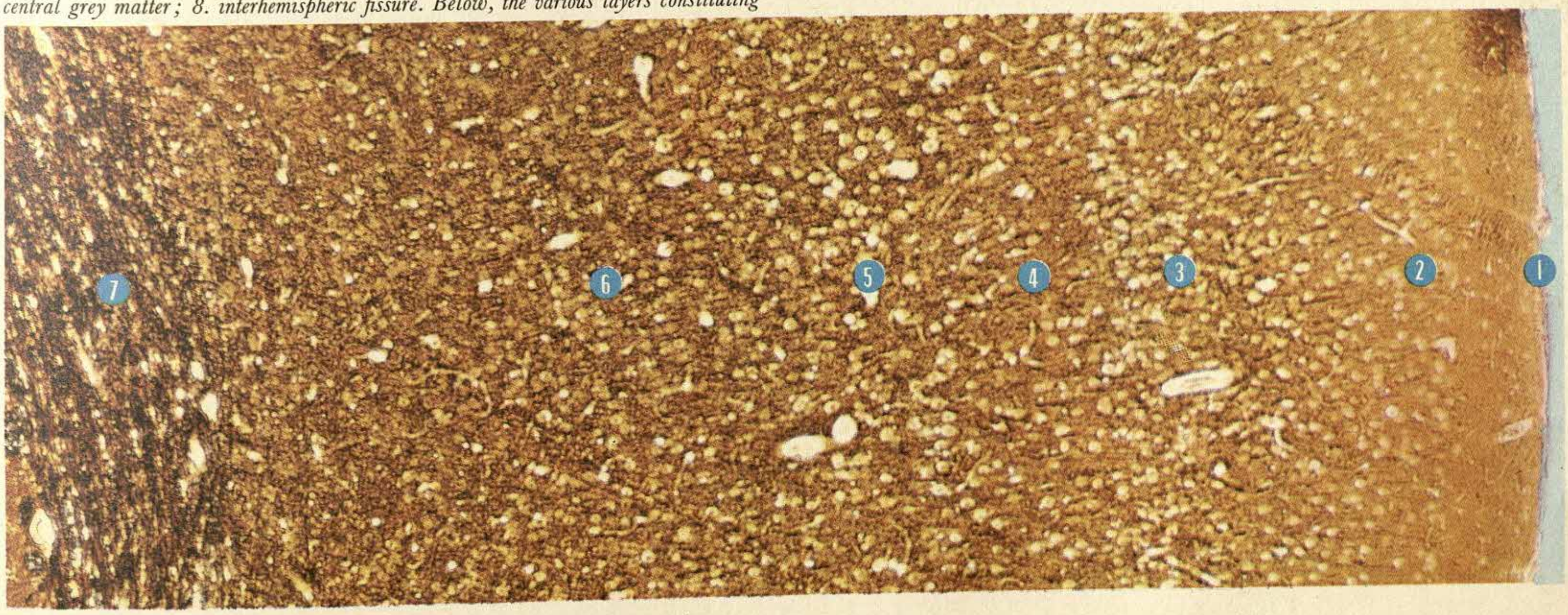
Conditioning is a special form of learning studied extensively by the Russian physiologist Pavlov, the classic example being the dog which learns to salivate in response to a bell if the bell has previously been presented together with food. Conditioning of the alpha rhythm in man was first observed accidentally, when taking motion pictures of a man having his brain waves studied while opening and closing his eyes. The alpha waves were blocked or arrested each time he closed his eyes. The camera was started just before the man was asked to open his eyes. Soon the sound of the camera starting was sufficient to cause the alpha wave response.

Systematic study of the conditioning of the alpha rhythm to an otherwise ineffective sound stimulus has shown that all the various complex forms of Pavlovian conditioning can be demonstrated by using the brain waves as a conditioned response, taking the place of the secretion of saliva in dogs. This has provided a valuable experimental tool for the study of learning processes in man and in animals. It shows that the brain waves, even though of simple form, are related to important complex functions of the brain which can be modified by experience.

When a local area of the brain is injured severely, eg, by a bruise or laceration due to a



*The brain is an area of unceasing electrical activity. This activity is displayed both in the area of the cortex (shown below) and in the cerebral mass (shown above). The sections shown are from the rat, but the general disposition of the human brain is not essentially different. Above, frontal section: 1. corpus callosum; 2. anterior commissure; 3. lateral olfactory tract; 4. lateral ventricles; 5. optic chiasma; 6. cortex; 7. central grey matter; 8. interhemispheric fissure. Below, the various layers constituting the cerebral cortex and the subjacent nerve substance. This is an enlargement of the area shown by the dotted line in the photograph above: 1. molecular layer; 2. external granular layer; 3. layer of small pyramidal cells; 4. internal granular layer; 5. large pyramidal cell layer; 6. plexiform layer; 7. corpus callosum. (Photo Lod, Embryology Laboratory, Faculty of Medicine, Paris).*



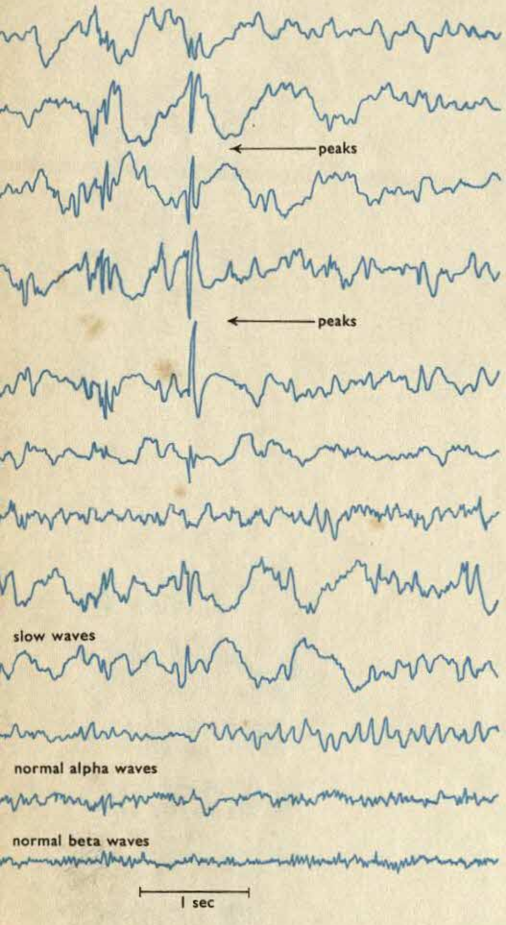


*Fig. 2. Electroencephalogram obtained with electrodes placed on the surface of the brain. Note the typical wave features (peaks) which denote the existence and location of the lesion to be removed, the slow waves emitted by the damaged part, and the normal alpha and beta waves (the three waves shown at the bottom) coming from the cortical areas adjacent to the lesion* ($1\ mm = 50\ \mu V$).

fracture of the skull, or damage by a brain tumour, changes in the electrical activity over that area may make possible its location by the EEG alone. If it is very severely damaged, there will be no brain waves; it will be electrically silent. With less damage, normal rhythms are replaced by focal slow waves, a sign of depressed function. If it is an irritative lesion, higher voltage waves appear—these may be quite rapid—called in some cases 'spikes'. When these local signs of irritation appear, the lesion may become a 'discharging' one, and result in the patient's having epileptiform seizures.

Lesions deep in the brain are not as easily located by the EEG, and may be missed completely if they do not cause enough disturbance to be picked up by the electrodes outside the skull.

The most dramatic changes occur in the EEG when patients are suffering from epileptic seizures or convulsions. It is in such conditions that the EEG is most useful. Even when the patient is not having an overt attack, the local or generalized 'epileptiform' electrical discharges can be detected in the EEG. Usually they are of much higher voltage than the normal waves; during a seizure they may reach 10 to 20 or 30 times the voltage of normal brain waves. Different kinds of seizure have different characteristic forms or locations of their electrical counterpart, the most characteristic being the so-called 'petit mal' seizure associated with a brief lapse of consciousness, as shown in fig. 1g. Such attacks may last for only 10 to 15 seconds. Normal electrical activity is suddenly interrupted over the entire head on both sides simultaneously, and large, regular 'spike and wave' forms appear rhythmically at regular intervals, 3 c/sec, synchronized as though triggered by a common pacemaker deep in the brain (see fig. 2). Experimental studies of the mechanism of this form of epileptic discharge have led to some important discoveries as to how brain mechanisms govern consciousness in normal individuals.

When it is possible to locate a focal area of brain giving rise to seizures, it may be possible to remove the damaged area and prevent the seizures. During such operations electrical activity can be recorded directly from the exposed surface of the human brain. Such direct records are called electrocorticograms. Since the patients operated upon do not have a general anaesthetic, the opportunities thus provided for direct study of the electrical activity of the exposed brain have given much precise information that cannot be obtained from the usual EEG. For example, the changes in electrical activity from the motor cortex were recorded directly, by Dr Penfield, while the patient was making voluntary movements of the hands.

Psychiatric disturbances in brain function, such as one finds in patients in mental hospitals, are often not associated with serious changes in the electrical activity of the brain as recorded by the EEG. Obviously, important aspects of brain activity may not be reflected in the brain waves picked up from its surface. What then is the true functional significance of brain waves?

## *The meaning of brain waves*

Actually, the true significance of electrical brain rhythms is not known. Physiologists are not certain how they are generated, nor in precisely what manner they are related to the discharge of brain cells, but they do know that they are influenced by the metabolic and functional processes of the brain.

Psychologists have speculated that the timing of certain mental processes in perception of visual stimuli may be related to the alpha rhythms, but evidence is inconclusive. The rhythms are sensitive indicators of states of consciousness, attention, and even learning processes, but just how they participate in the intimate mechanisms of such processes is not known.

Certainly, electrical 'brain waves' should not be confused with ideas or thought processes, nor can they be implicated in pseudo-scientific notions about the transfer of thoughts from one person to another (telepathy).

In fact, the electrical waves of the brain surface do not represent the discharge of brain cells. They represent electrical activity of a different sort, generated in thousands of fine nervous processes or synapses. Only the statistical derivative of this activity appears on the surface, dependent upon the synchronization of radially-oriented electrical dipoles. When this synchronization is disturbed, as during activation of the cortex, the rhythmic waves on the surface often disappear, or become 'desynchronized'. This gives rise to the paradox of less apparent electrical activity when the brain is actually more active.

Even with the most highly refined modern electrophysiological techniques and mathematical computers, we have a very long way to go before we understand how the electrical activity of the brain can be related to intimate mechanisms of human thought and behaviour.

# The neurophysiological basis of mind

*Sir John ECCLES*

The preceding pages have given an introduction to the topography and fine structure of the cerebral cortex and to the way in which it works. I say 'works' deliberately, because we have to think of the brain as a machine—by far the most complicated machine in existence: infinitely more complicated than the most complex man-made machines, the electrical computers.

For our present purpose it is sufficient to regard the cortex as being formed by neurones arranged in a plate about 3 mm thick and 2,000 sq cm in area. The constituent neurones have a wealth of functional connections between themselves and also with incoming fibres from other cortical areas and the basal ganglia of the brain (fig. 1). The profusion of cellular interconnection in the grey matter is beyond all imagination. In each square millimetre of the cortex there are about 50,000 nerve cells (neurones) and each probably connects synaptically[1] with as many as a hundred other cells and receives synaptic connections from a similar number.

The neurone is a functional unit because transmission from its receptive sites (the synaptic endings on it) to its effector sites (the multitude of synaptic endings made by its axon) occurs by the propagation of an all-or-nothing[2] impulse. A neurone generates an impulse when it is bombarded by a sufficient number of excitatory impulses in such quick succession that it is depolarized to a critical level. Equally important factors in neuronal control are the inhibitory synapses, which are interspersed with the excitatory ones over the neuronal surface membrane. Activation of inhibitory synapses has the opposite effect on the membrane potential, increasing it above the normal level, and so actively counteracting the depolarizing action of excitatory synapses. Thus, convergence of excitatory and inhibitory synaptic action on any one neurone results in an algebraic summation of the opposed changes in membrane potential, depolarization and hyperpolarization respectively, the release of an impulse occurring when the net depolarization attains the critical level for generating a discharge, which is at about 61 mV.

The time involved between the arrival of excitatory impulses at synapses and the consequent generation of an impulse may be considerably less than one thousandth of a second (a millisecond) (fig. 3).

Essentially we can consider the behaviour of the cerebral cortex as being an integral of the behaviour patterns of each of its ten thousand million neurones. From the nature of neuronal transmission, as outlined above, there are both spatial and temporal factors in this integration. When a neurone discharges an impulse down its axon, it exerts synaptic action on other neurones and so is potentially capable of modifying the spatio-temporal pattern of behaviour of the cortex. While it is quiescent, it contributes nothing to the pattern. Thus, so far as its contribution to the patterned activity of the cortex is concerned, there are just two states of a neurone, activation by an impulse, or quiescence. In this respect it resembles a digital computer, but otherwise the analogy is not helpful.

The way in which spatio-temporal patterns of activity develop and spread in the cerebral cortex has been studied most effectively in isolated slabs of cortex, where a few million neurones have been cut off from all connection with the rest of the brain and yet have their blood supply intact. As a rule, all cells are quiescent in such a slab, but rhythmical activity of several seconds' duration can be evoked by electrical stimulation: Delisle Burns has shown that impulses are then transmitted along neurones arranged in the closed self-re-exciting chains described by Lorente de Nó, so giving reverberatory circuits of activity. Since the convergence of many impulses on any neurone is required to make it discharge, propagation would not occur through a chain composed of a serial arrangement of single neurones. Rather, the propagation would resemble an advancing wave-front of multi-lane traffic formed by the activation of many

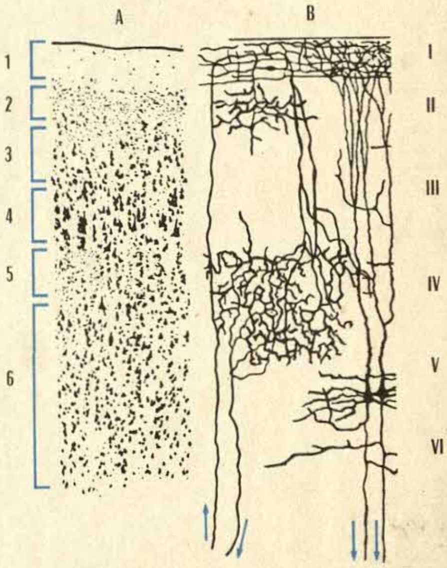


*Fig. 1. Vertical section of the cortex, showing the six cell-layers of neurones. A, cell bodies; B, group of complete neurones (cell bodies and fibres). At the level of layer V are large pyramidal cells whose axons spread out at the top of the cortex. Note the bushy expansions of certain descending fibres of layer I; other fibres run upwards.*

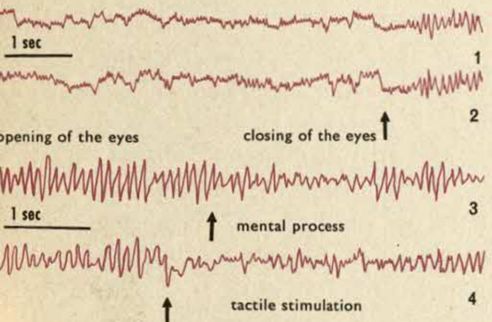


*Fig. 2. The alpha rhythm disappears when a person opens his eyes (first arrow) and recommences when they close again (second arrow). The phenomenon was recorded simultaneously through its effects on the right (1) and the left (2) occipital poles of the human brain. The similarity between the encephalograms is clear. When a person engages in a mental calculation (curves 3 and 4), the afferent stimulation (arrow) temporarily interrupts the alpha rhythm.*

cells in parallel for each synaptic linkage in the chain, but this analogy must not be taken to imply a too regimented advance in strict unison.

It is difficult to conceive the complexity actually obtaining in propagation over neuronal chains where each neurone could perhaps be linked to a hundred other neurones, and where the convergence of ten or more impulses within a few milliseconds would be necessary in order to make any one neurone generate an impulse. It is therefore desirable to study the properties of simple models of networks. For example, fig. 4 represents such a model formed by the synaptic connections between 16 cells. Simplification has also been achieved by neglecting inhibitory action and by reducing the number of excitatory synapses made by each axon to no more than three. Correspondingly, it has been assumed that any cell is made to discharge by the activation of two or more synapses on its surface.

Fig. 4 also illustrates other features of a neuronal network. For example, if there is inadequate convergence at any stage of the advancing wave-front, the wave will be extinguished. It will also be noted that along the fringe of an advancing wave-front there are subliminally excited neurones. Such 'fringe neurones' give opportunity for growth of a wave if other influences should also subliminally activate them.

Thus we are introduced to the concept of instability of a wave-front. It may be diminished by inhibitory or depressant influences and so ultimately be extinguished, or it may be enhanced by factors aiding the activation of 'fringe neurones'. It will also be appreciated that, if a wave-front moves into neuronal pathways having interconnections of suitable configuration, it may bifurcate into two waves propagating independently; while, conversely, two wave-fronts propagating at the same time into the same pool of neurones would coalesce and give an onwardly propagating wave having features derived from both waves, with additional features due to the summation.

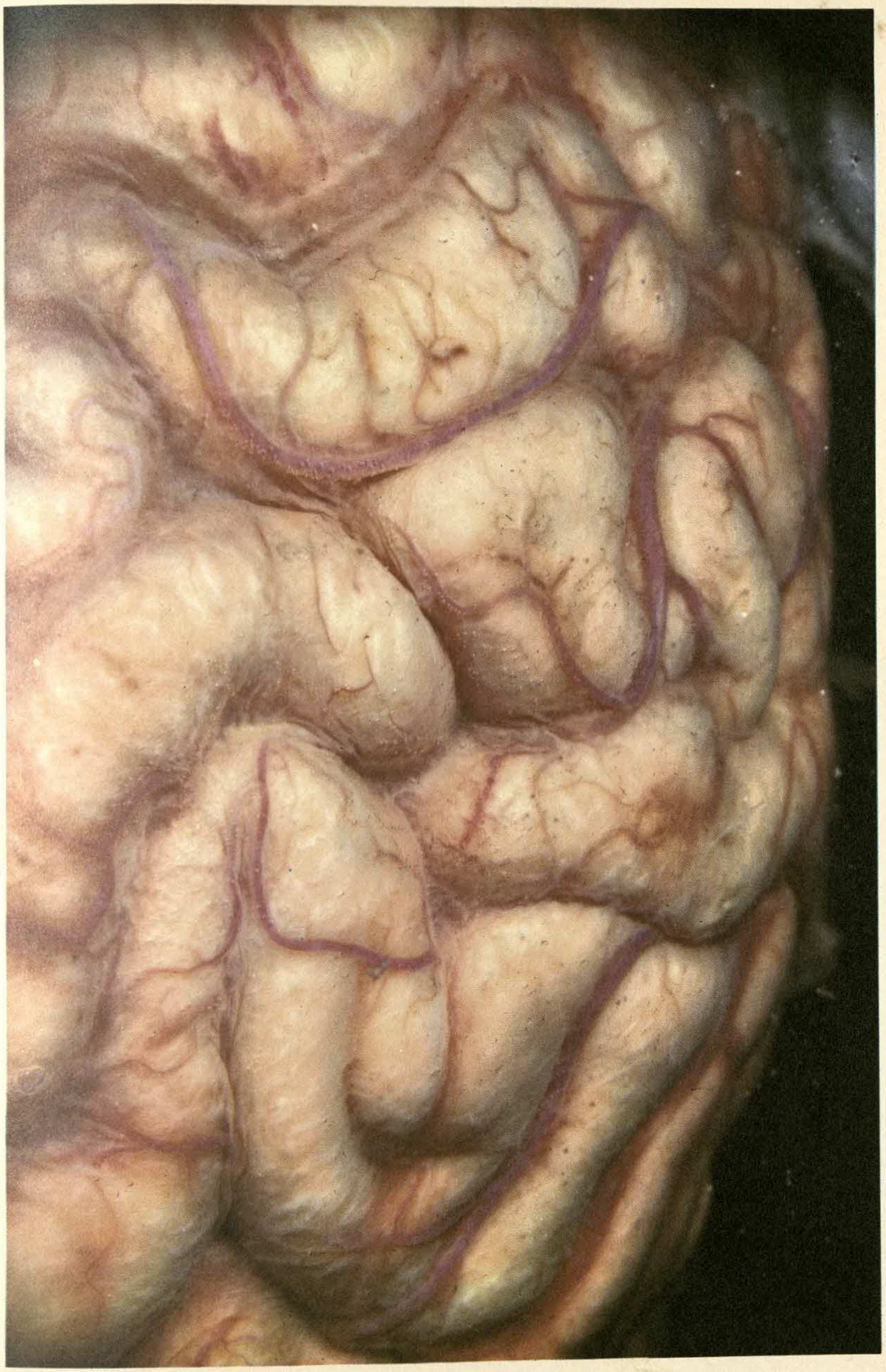
It will be realized that in the neuronal network of the cerebral cortex the factors involved in transmission of a wave-front are vastly more complicated than in the simplified model of fig. 4. In the first place, each neurone would make very many synaptic contacts with other neurones, and also receive many more—perhaps as many as a hundred. As indicated in fig. 3, activation of ten or more synapses within a few milliseconds would be required to make any one cell discharge an impulse and become an active agent in the advancing wave-front. Perhaps as many as one hundred neurones would be involved in each stage of the advancing wave-front, so that an advancing wave would sweep over 100,000 neurones in one second.

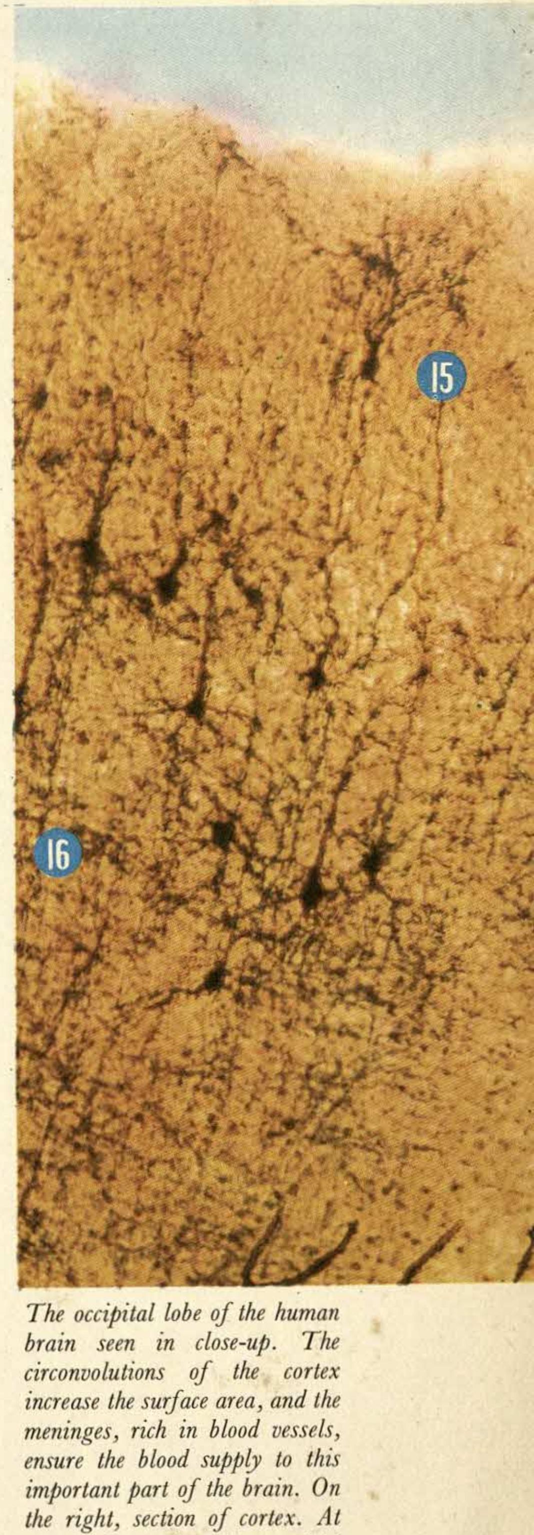
## *The electrical responses of the cerebral cortex*

We are now in a position to attempt an interpretation of the electrical responses that lead from the surface of the cerebral cortex and were described in a previous chapter. During inattentive but awake states, the predominating rhythmic wave of the electroencephalogram,[3] as it is called, is about ten a second, the alpha rhythm (fig. 2). The rhythmic character is readily explained by the circulation of impulses in reverberatory circuits with a circuit time of about 0·1 sec, which corresponds approximately to the duration of the increased membrane potential that Phillips observed to follow the discharge of a pyramidal cell. It has been shown by Bremer and Magoun that to maintain even the low activity giving the alpha rhythm, the cortex must be subjected to a continuous excitation by impulses from lower centres, or its activity virtually ceases and it lapses into deep sleep.

When the brain is active, for example, during some vivid sensory experience, or during concentration on a problem or a skilled action, the alpha waves give place to fast, irregular ripples. Evidently, the increased activation of the cortical neurones by the immense afferent barrage from the retina (fig. 2a), or by intense mental activity (fig. 2d) prevents their phasic activation at about ten a second, and this effect must be exerted over a large area of the cerebral cortex. The intensity of synaptic bombardment must then be adequate to evoke neuronal discharges at intervals much shorter than the 100 msec needed for a virtually full recovery of excitability. Moreover, it may be assumed that there are specific spatio-temporal patterns of neuronal activation, ie, the diffuse random activation at low intensity is replaced by specific patterns of activation of high intensity, such as those represented in fig. 5. Since the cerebral activity is recorded from the immensely complicated neuronal network immersed in a volume conductor (the tissue of the brain, skull, etc), relatively high voltage waves would be expected only when large numbers of neurones are activated in phase, as is assumed

# The cortex





*The occipital lobe of the human brain seen in close-up. The circonvolutions of the cortex increase the surface area, and the meninges, rich in blood vessels, ensure the blood supply to this important part of the brain. On the right, section of cortex. At 15, the layer of small pyramidal cells; at 16, the large pyramidal cells and their prolongations. (Photo Lod, Embryology Laboratory, Faculty of Medicine, Paris).*

(1) Synapse: *the point of junction between two neurones.*

(2) All-or-nothing law: *a principle which applies as much in the physical as in the biological sciences, according to which a precise event takes place when a certain 'threshold' is exceeded, the occurrence of the event being impossible below this threshold, but occurring automatically, without variation in intensity if the threshold is crossed, no matter by how little.*

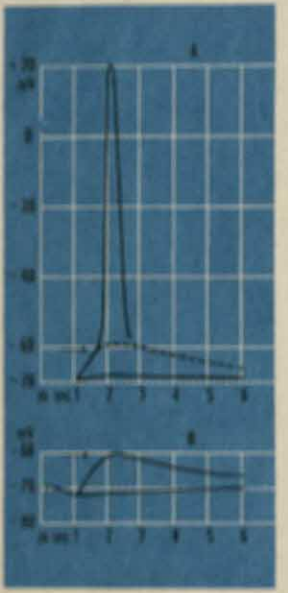


*Fig. 3. Electrical responses of a nerve cell obtained by inserting a microelectrode into the interior of the cell. The resting membrane potential is −70 mV. When a single synapse is stimulated, a slight fall in potential lasting several milliseconds is recorded (lower black curve). Several synchronous actions additively give a much greater wave of potential (dotted curve) which, on reaching about 10 mV, gives rise to the action potential of the neurone (large spike). At B is seen an inhibitory synaptic potential of opposite direction which precedes the excitation potential (lower full line) and which is capable of preventing the functioning of the cell by diminishing the synaptic depolarization.*

for the alpha rhythm, while intense and finely patterned activity would give merely the ripples of very small amplitude.

We may picture the irregular ripples as being due to the specific spatio-temporal patterns woven by a multitude of travelling waves in the neuronal net[4] (fig. 6).

## *The perceptual activity of the cerebral cortex*

In attempting to appreciate the cortical events occurring during some very simple sensory experience, eg, a touch on a small area of skin, it is necessary to understand the way in which the information is conveyed with a sufficient degree of specificity for the subsequent cortical interpretation. As Adrian first showed, receptor organs signal by a coded arrangement of impulses, like a Morse system of dots only, and this specificity of discharge is preserved through the sensory pathways up to the cortex, so that it can be observed in the responses of single neurones of the cortex, as shown by Jung, Mountcastle, Hubel and others, for the visual and cutaneous receptors. The different kinds of modality of sensory stimulation, eg, touch, pressure, joint movement, activate different sense organs, each with its own specific lines to the cerebral cortex. It has been found by Mountcastle that, initially, each modality activates neurones in narrow vertical columns that are arranged as an interdigitating mosaic in the cortical map. For our present purpose it is sufficient that impulses discharged from receptor organs with different modalities and locations primarily activate different assemblages of neurones in the cortex.

Beyond this stage virtually nothing is known about the evolving patterns of cortical activity, but one can speculate that the specificities are preserved in the character of the respective wave-fronts propagating through the neuronal network. One can further presume that the integration of the information relayed from receptor organs of various locations and modalities is effected by interaction between, and synthesis of, the several propagating waves of neuronal activation, to give some unique spatio-temporal pattern of neuronal activity. For example, such a pattern of activation could be characteristic of pressure on a certain area of skin with modalities signalling cold and joint sensation also integrated, so that the assembled wave form would be characteristic of a smooth cold surface of a certain shape, eg, of a stone. We have now further to realize that integration occurs between the most diverse receptor organ discharges, eg, from eye and hand, or from eye and ear.

This correlation and integration of information from diverse sense organs can be conceived only in terms of the neurophysiological concepts of partial confluence and interaction of the spatio-temporal patterns of neuronal activation evolving out of the cortical input from the various sense organs; that is, not only have we to envisage the confluence of patterned activities stemming from one type of sense organ, eg, of the various sensory modalities in one skin area, but also information from any sense organ has potentially to be capable of integration with that from any other. The manner of this integration is illustrated in fig. 6: the fusion of elements deriving from both the red and yellow patterns of neuronal activation gives the orange pattern.

## *Memory and imagery*

Our present problem relates to the recall of some sensory experience which we may term imagery or memory. Memory must be dependent on some enduring change that has been produced in the cortex by its previous activation. Currently there are two hypotheses as to the nature of this enduring change: that impulses are circulating through some specific spatio-temporal network; and that the initial activation of synapses causes some structural change whereby they become more effective. The first explanation can now be rejected except for memories enduring for a few minutes, since it has been found that memories survive the suppression of all activity of the neurones in the cerebral cortex in conditions of deep anaesthesia, concussion and extreme cold. According to the second explanation, activation of synapses causes an enduring increase in their efficacy. The initial sensory input enhances the function of the synapses that are activated in the spatio-temporal pattern of neuronal excitation. An experience may not be remembered if a cerebral trauma (concussion or electric shock) is applied as much as twenty minutes later.

We may say that the remembered image is experienced while its specific spatio-temporal pattern is being replayed in the cortex. It may therefore be postulated that the initial development of effectiveness in certain synaptic junctions is a sequel to the primal event that is remembered, and this effectiveness is sustained and even enhanced by each subsequent replaying in the brain (and remembering in the mind).

The physiological equivalents to memory are the conditioned reflexes, which have now been shown to produce characteristic changes in the electroencephalogram. These changes are often observed over large areas of the cortex, and may be assumed to be due to spatio-temporal patterns of neuronal activation that are spreading widely in the cortex along specific paths laid down during the conditioning.

It is sufficient to consider the increased synaptic function as giving a 'congealed' neuronal pattern or engram[5] ready to be replayed by an appropriate input. The postulated change is in the presynaptic component of the synapse, not in the postsynaptic.

These postulates of engrams accord well with one's experiences of remembered imagery. By far the best evocative situation arises from some closely similar experience. Here the evolving spatio-temporal patterns will tend to correspond closely to the original, congealed pattern; hence the stage is set for the entry into, and the replaying, of this old pattern, as shown in fig. 6, at the points for the interaction and fusion between red and yellow patterns, to the exclusion of the black pattern.[6]

Thus in summary we may say that the memory of any particular event is dependent on a specific reorganization of neuronal associations (the engram) in a vast system of neurones widely spread over the cerebral cortex. Lashley has convincingly argued that 'the activity of literally millions of neurones' is involved in the recall of any memory. His experimental study of the effects of cortical lesions on memory indicates that any particular memory trace or engram has multiple representation in the cortex. Furthermore, Lashley concludes that any cortical neurone does not belong exclusively to one engram, but on the contrary, each neurone and even each synaptic junction can be built into many engrams. Already it has been shown diagrammatically in fig. 4 that two separate patterns of neuronal activation can spread through the same assemblage of neurones and emerge each with its own identity; this is further illustrated by the crossing paths in fig. 5.

These figures illustrate at the simplest level the way in which any one cortical neurone takes part in the propagation of many diverse spatio-temporal patterns. The necessity for such an economy will be appreciated in view of the conclusion that millions of neurones form the engram of the simplest memory, otherwise our brains would have the capacity for only a few thousand simple memories. Our potentialities must be at least hundreds of times more. We can picture any one highway of multi-lane traffic through the neuronal network as repeatedly crossing through neuronal networks common to other multi-lane highways.

Strictly speaking, all these patterned activities are woven in the three-dimensional neuronal network, the diagrammatic drawings (figs. 4, 5 and 6) having much the same significance as with chemical formulae. We have to envisage a patterned activity as being formed by the curving and looping of a wave-front through a multitude of neurones, now sprouting, now coalescing with other wave-fronts, now reverberating through the same path—all with a speed deriving from one thousandth of a second for a relay, the whole wave-front advancing through perhaps one million neurones in a second. Such are the patterns woven on the magic loom of Sherrington. Recognition of some simple idea—a tune or a word or forms such as triangles and circles—would depend on the activation of spatio-temporal patterns resembling those activated in the previous experience of this idea, with the consequence that there would be likely to be a similar outcome in some behaviour pattern.

## *Mind-brain liaison*

The concepts so far considered relate merely to the two sides of the apparently unbridgeable gulf that lies between the matter-energy system of the brain and the non-sensual concept of the mind, which latter has remained unassimilable into the matter-energy system. We have been able to give in rough outline an account of the specific events in the brain which are linked with specific mental experiences, but nothing has yet been said concerning the 'how' of that linkage. We shall approach this problem by first considering problems in perception.

### 1. *Neurophysiological problems in perception*

The usual sequence of events is that some stimulus to a sense organ causes the discharge of impulses along afferent nerve fibres, which, after various synaptic relays, eventually evoke specific spatio-temporal patterns of impulses in the neuronal network of the cerebral cortex. The transmission from sense organ to cerebral cortex is by a coded pattern that is quite unlike the original stimulus, and the spatio-temporal pattern evoked in the cerebral

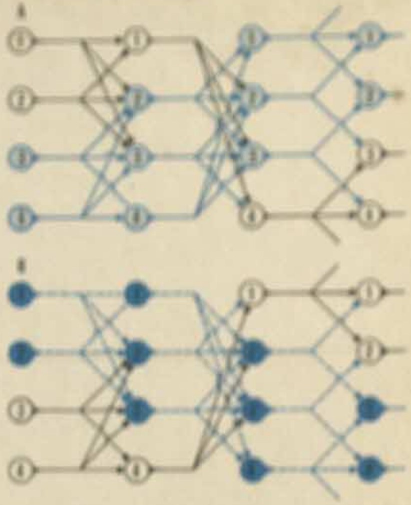


*Fig. 4. Diagram of a neurone net, showing how the waves can be propagated along channels with multiple paths in the cortex. Each cell body gives off an axon (towards the right), having up to three branches and which transmits the impulse as far as the cell bodies of the neighbouring column; at least two synapses must enter into action for a cell to emit or relay the impulse. Activated cells and fibres are shown in black or in colour. The diagram shows how two distinct incident waves (eg. $A_1$–$A_2$ in the black circuit, $A_3$–$A_4$ in the coloured circuit) can travel, using the same cell connections, crossing one another, and finally emerging in quite different forms ($B_3$–$B_4$ in the black circuit, $A_1$–$A_2$ in the coloured circuit).*

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(5) *See 'Electrical Activity of the Brain', p. 71.*

(6) *According to the felicitous definition of Sherrington, this network is an 'enchanted loom where millions of flashing shuttles [the nerve impulses] weave a dissolving pattern, always a meaningful pattern though never an abiding one; a shifting harmony of sub-patterns'.*

(7) Engram: *In neurophysiology, as in cybernetics or information theory, engram is the term applied to a stereotyped model which the machine (or here, the brain) reproduces without modifying it.*

(6) *In less favourable situations, when trying to recall this or that image, we make use of various mnemonic tricks, deliberately choosing sensory stimuli or trains of thought suitable for this purpose. It is a frequent practice to which we have completely accustomed ourselves. We have but to think of the means which we use to remember a tune, a sight, a name, or an event.*

(7) *Personal experience, beginning in earliest infancy, and intercourse between one observer and another, are the normal means by which we learn to interpret our intimate perceptual experiences as events taking place in a unique physical universe common to all observers. In point of fact, a long period of apprenticeship is necessary before cerebral events resulting from retinal images are interpreted as prolongations of a spatial world and can thus be utilized to take cognizance of that world.*

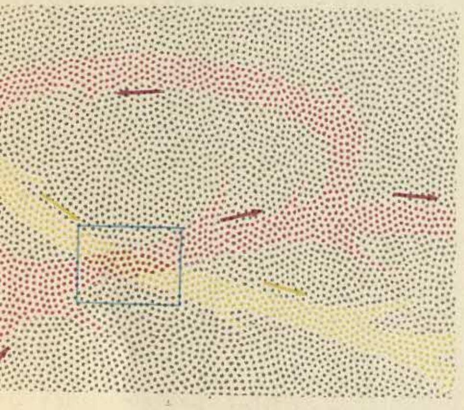

*Fig. 5. Diagram of the mutual relations of the channels in a cortical circuit, the details of which correspond to fig. 4 (blue rectangle). Each red dot represents an active neurone, each yellow dot an inactive one. When the two channels cross, they utilize the same group of neurones, but they enter and leave it in different directions (as in fig. 4). Note, on the one hand, the coalescence of the paths; on the other, that the bifurcating branches often come to nothing. The return circuit of the red channel is also seen; it is responsible for the phenomenon of resonance.*

cortex would again be different. Yet, as a consequence of these cerebral patterns of activity, we experience sensations (more properly the complex constructs called percepts) which in our private perceptual world are 'projected' to somewhere outside the cortex; it may be to the surface of the body or even within it, or, as with sight, hearing or smell, to the outside world. However, the only condition necessary for an observer to see colours, hear sounds, or experience the existence of his own body, is that appropriate patterns of neuronal activity shall occur in appropriate regions of his brain.

Further problems are, of course, involved in attempting to understand how these brain events can give us valid experiences of an external world. However, by various means of communication, all the observers, each with his private and unique perceptual world, come to agree on the existence of a single physical world, which provides an explanation more or less complete and satisfactory, of these manifold perceptual worlds.[7]

### 2. *Postulate of the dynamic properties of the cortex*

There is one partial approach to the key problem of the 'how' of mind-brain liaison that hitherto has not been essayed. It is here contended that a special property is exhibited by the dynamic patterns of neuronal activity that occur in the cerebral cortex during conscious states; and that the brain, by means of this special property, enters into liaison with mind, having the function of a 'detector' that has a sensitivity of a different kind and order from that of any physical instrument. We are envisaging the pattern of activity in the cortex at any instant as being determined by two factors: (i) the immediate (and very recent) input of afferent nerve impulses; (ii) the developed structural specificity (inherited and acquired).[8]

### 3. *Neurological approach to the problem of 'freedom of the will'*

The special detector properties of such a neuronal network will be discussed in giving an explanation of the way in which the spatio-temporal patterns of activity *could* be modified by a 'mind influence' or 'will'. It is a psychological fact that we believe we have ability to control or modify our actions by the exercise of 'will', and in practical life all sane men assume that they have this ability. By stimulation of the motor cortex of a conscious human subject it is possible to evoke complex motor acts. The subject reports that the experience is quite different from that occurring when he 'willed' a movement. As pointed out by Sherrington, the distinction arises not in the differences between the movements, but in their different antecedents. In the one case there was the experience of having 'willed' an action, which was missing in the other.

It is not here contended that all action is willed. There can be no doubt that a great part of the skilled activity devolving from the cerebral cortex is stereotyped and automatic, and may be likened to the control of breathing by the respiratory centres. But it is contended that it is possible voluntarily to assume control of such actions, even of the most trivial kind, just as we may within limits exercise a voluntary control over our breathing.

An important neurophysiological problem arises as soon as we attempt to consider in detail the events that would occur in the cerebral cortex when, by exercise of 'will', there is some change in response to a given situation. We can say firstly that, assuming 'will' to be operative, there must be a changed pattern of discharge from the motor control down the pyramidal tract and so to the motor-neurones controlling movement. Presumably this change is brought about because there is a change in the spatio-temporal pattern of influences playing upon the pyramidal cells in the motor cortex.

The problem of the mode of action of the 'will' can be simplified and sharpened by considering first the behaviour of a single neurone in the active neuronal network of the cortex. Suppose some small 'influence' were exerted on one of the synapses on its surface that would make a neurone discharge an impulse at a level of synaptic excitation which would otherwise have just been ineffective; that is, in general to raise the probability of its discharge. Such a discharged impulse would in turn have an excitatory effect on all the other neurones on which it impinges, raising the probability of their discharge. If we assume, as above, that the transmission time from neurone to neurone occupies 1 msec, a spread to a large number of neurones is possible in, say, 20 msec, a time that is chosen because it is at the lower limit of duration of discrete mental events.

Calculations on the basis of knowledge of the wealth of neuronal connections have suggested that in the active cerebral cortex hundreds of thousands of neurones could be affected in 20 msec by a discharge originating in any one. In order to apply these calculations to our problem of how 'will' *could* act on the cerebral cortex, it is necessary to take into account the evidence that 'will' can act on the cortical neuronal network only when a considerable part of it is at a relatively high level of excitation, ie, we have to assume that, for 'will' to be operative, large populations of cortical neurones are subjected to a considerable synaptic bombardment and are stimulated thereby to discharge impulses which bombard other neurones. Under such conditions it may be conservatively estimated that, out of the hundred or more synaptic contacts made by any one neurone, at least four or five are *critically effective* (when summated with synaptic bombardments by other neurones) in evoking the discharges of neurones next in series. The remainder would be ineffective because the recipient neurones would not be poised at this critical level of excitability. This ineffectiveness of the recipient neurones would be attributable either to a too low level of excitation, or to a too high level, so that the neuronal discharge occurs in any case, without this additional synaptic bombardment. Thus at any instant the 'critically poised neurones' would be the effective detectors and amplifiers of the postulated action of the 'will'.

We may say that in the active cerebral cortex, within a period of 20 msec, the pattern of discharge of even hundreds of thousands of neurones would be modified as a result of an 'influence' that initially caused the discharge of merely one neurone. But further, if we assume that this 'influence' is exerted not only on one synapse of the active network, but also on the synapses of a wide field of neurones in some sort of spatio-temporal patterning, then it will be evident that potentially the network is capable of integrating the whole aggregate of 'influence' to cause modification of its patterned activity, which otherwise would be determined by the pattern of afferent input and its own inherent structural and functional properties. Such integration would occur over hundreds of thousands of neurones in a few msec, the effects exerted on any and every neurone being correlated in the resultant patterned activity of the surrounding hundreds of thousands of neurones. Thus, in general, the evolving spatio-temporal pattern of activity would be determined not by two factors as stated provisionally above, but by three factors: (i) the micro-structure of the neuronal net and its functional properties; (ii) the afferent input; (iii) the postulated 'field of extraneous influence'.

No physical instrument would bear comparison with the postulated performance of the active cerebral cortex as a detector of minute 'fields of influence' spread over a microscopic pattern and with temporal sequences of msec. The integration, within a few msec, of 'influences' picked up at hundreds of thousands of synapses would be unique, particularly when it is remembered that the integration is no mere addition, but is exerted to modify in some specific way 'a shifting harmony of subpatterns' of neuronal activity, achieving expression through the modifications so produced.

Thus, the neurophysiological hypothesis is that the 'will' modifies the spatio-temporal activity of the neuronal network by exerting spatio-temporal 'fields of influence' which become effective through this unique detector function of the active cerebral cortex. It will be noted that this hypothesis assumes that the 'will' or 'mind influence' has itself a spatio-temporal patterned character in order to allow it this operational effectiveness.

### 4. *Cortical activity and consciousness*

When the cortex is at a low level of activity, it would function inefficiently as a detector, and presumably also as a transmitter, on account of the small proportion of neurones poised at the critical level of excitation and the consequent improbability of an effectively spreading influence; hence an explanation is provided for the invariably observed failure of mind-brain liaison when the electroencephalogram reveals depressed cortical activity. But it is of great interest that an explanation is also provided for the loss of consciousness in the stereotyped and driven cortical rhythms that occur in convulsions, for the neurones of the cortical network would also then lack the critical poise as well as the specific patterning. In convulsions it may be assumed that the neurones are excited at a high level by the intense convergence of impulses travelling over stereotyped pathways.

It is further to be noted that, according to the hypothesis, only a part of the cortex is needed for liaison with mind. It may be that any area that is in the critical excited state will suffice. This corresponds to the clinical evidence that mind-brain liaison is not interrupted by excision of a large part of the cerebral cortex, or when a large part is occupied by activity that excludes liaison; for example, by a convulsion or even by alpha-wave activity, as suggested by Adrian. Maybe less than a tenth of the cortex in the right state of activity would be enough to give an effective mind-brain liaison.

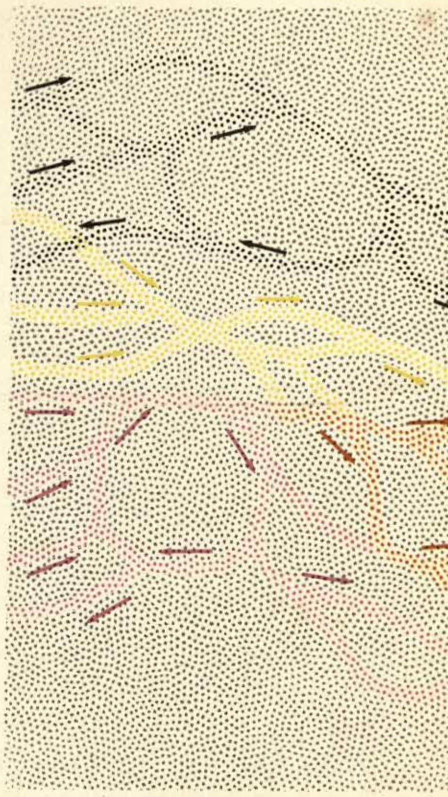

*Fig. 6. Diagrammatic expansion of fig. 5. Three nerve channels are shown, in order to indicate the loops, the bifurcations and the fusion of a circuit corresponding to a particular mental process. It is likewise seen how the integration of two channels (yellow and red) gives rise to a composite experience, the 'information' coming from two different sense organs being integrated into a spacial-temporal configuration (orange) which unites the characteristics of each of the two paths. The direction of the wave is shown by the arrows.*

(8) *In support of this hypothesis, it can be pointed out that the function of the network is always unconscious when cortical activity is zero, weak (sleep, coma, anaesthesia), or stereotyped (epileptic convulsions, effects of shock); this is borne out by encephalograms. In other words, there are states in which the neurone network is not in connection with the mind.*

# The mechanism of vigilance

*Vincent BLOCH*

*When we try to establish classifications of conduct, of the 'behaviour' of an animal or of man, we must have recourse either to the goal at which that behaviour is aimed or to the motive behind it. We can thus define a certain number of specific types of behaviour, such as flight or attack, the search for food or for a sexual partner, the acquisition or forgetting of new modes of behaviour, intelligent adaptation to new situations, language, etc. But these types of behaviour cannot be altogether reduced to this specific, qualitative aspect; they also have another dimension, that of intensity.*

Activities directed at the same goal can either be undertaken with little expenditure of energy, in a sleepy state, or on the contrary, with great expenditure of energy, in a state of extreme alertness. We can thus place such activities on a scale of intensity, of which the extremes would be represented by a deep sleep on the one hand and the excesses of anger on the other. Present-day physiologists talk not of intensity but of 'degree of activation', a term which encompasses both the increased activity of the nervous system and also the intensification of the organic activities which are the result of it.

The extent and the complexity of the relations between an organism and its external environment are an approximate function of the degree of activation. During sleep, we are almost unaware of the world around us; on the other hand, states of sustained close attention exact a high degree of activation. It is for this reason that variations in the degree of activation are often described by their consequences on behaviour, ie, by variations in the degree of vigilance.

During the last few years, physiologists have discovered the existence of nervous mechanisms which are essentially responsible for the regulation of vigilance. At the base of the brain, in the median region of the brain-stem and extending from the medulla to the hypothalamus, one finds a structure known for a long time by anatomists as the *reticular formation.* This formation takes its name from its structure, which is like a network. It is made up of a large number of nerve cells (these constitute nine-tenths of the total in the brain-stem), interlinked and connected by a network of junction cells. The reticular formation, which exists in all vertebrates and whose importance grows with each level in the animal scale, was until recently a *terra incognita* on the maps of the nervous system. Contemporary research has shown that this structure acts as a sort of distributor of 'nervous energy'. This 'energy' is at first drawn from the external environment in the form of centripetal nervous impulses which come from the sense organs (and in the internal environment through the proprio- and interoceptive nerve endings) and it is then distributed to the whole of the body in the form of centrifugal nervous impulses which produce facilitating effects on the musculature, the autonomic nervous system, and the cerebral cortex.

The reticular formation is the site of convergence of all the sensory pathways. Nerve fibres leave each type of sense receptor, such as the eye, the ear, the tactile corpuscles, the receptors for tension and movement in muscles, etc, and after a certain number of relays they reach specialized regions of the cerebral cortex. These fibres carry the nervous impulses which keep us informed of every change in the external environment or of our position in relation to this. But these same fibres, as they pass along in the region of the brain-stem, send off collateral fibres which run into the reticular formation. Electrophysiological techniques enable us to show that nervous impulses coming from receptors of different types may end up at the same place in the formation. Thus these impulses, deriving from the collateral branches, lose their specific character; they no longer have a role in giving information. We shall see that in fact they have a dynamogenic role. Thus every stimulus to the body fulfils a double role: it gives us specific information through the specialized channels, and at the same time it produces 'energy' through this diffuse structure which is the reticular formation.

The reticular formation, which is always being bombarded by incoming sensory impulses, has therefore an activity of its own. This activity is equally maintained by means of chemical reactions. It is increased, for example, if the concentration of carbon dioxide or of adrenalin in the blood increases. Thus it is closely linked with the homœostatic mechanisms of the body.

The level of activity in the reticular formation—we might say its 'tone'—must show variations in relation to the rate of excitation that it receives. These facts give substance to the idea of the level of activation which was discussed earlier.

The energy which is thus accumulated by the reticular formation is redistributed to the body in the form of impulses which originate in the structure and are transported by the pathways radiating in all directions. We know in fact that pathways from the reticular formation (reticulo-fugal pathways) reach the cerebral cortex, the neurones which send impulses to the muscles, the sympathetic system, etc. These impulses originating in the reticular formation have facilitating effects on the structures they reach. Therefore, an activation of the reticular formation leads to an increase of cerebral activity, a lowering of the threshold for the starting of movements, and an increase in visceral functions. As far as behaviour is concerned, such a process allows richer and more numerous exchanges between the organism and its environment; in other words, it leads to a heightening of vigilance.

## *The role of the reticular formation*

Experimental proofs of the part played by the reticular formation in the regulation of vigilance are numerous. The production of widespread lesions of this region in experimental animals leads to a state resembling sleep. Also, it has been shown that the barbiturates, a family of hypnotic drugs, act on the reticular formation. Examination of the records of the electrical activity of the cerebral cortex (electroencephalogram) shows that there is a marked resemblance in the frequency and form of variations of the potential during natural sleep, during that due to barbiturates, and in the state which follows lesions of the reticular formation.

It is possible to introduce fine electrodes into the reticular formation of sleeping animals and then to excite them by means of small alternating currents. When this is done, the animals wake up, their movements are facilitated, and the effects on the sympathetic nervous system are increased. At the same time, the activity shown on the electroencephalogram changes and the slow waves of large amplitude, characteristic of sleep, are replaced by smaller, more rapid, waves of weaker tension, characteristic of the waking state.

Such excitation can be induced in animals which are not anaesthetized and are free to move. This is done by implanting electrodes under anaesthesia in a previous operation and fixing them firmly. They are coupled by flexible wires to the apparatus for producing the stimulating current. In such animals, which may be monkeys, cats or rats, for example, it is possible to increase very gradually the intensity of the current. This increase in the stimulation corresponds to successive changes in behaviour which can be classified according to the scale of intensity of which we spoke earlier. A simple awakening of attention without movement is succeeded by slight exploratory activity and then this activity gradually increases until it reaches a vigorous and unco-ordinated agitation when the excitation current is very strong.

In as much as they have shown this to be a structure responsible for regulating the state of wakefulness, such discoveries make the idea of a 'sleep centre' superfluous. At first sight, this would seem to bring the physiologist's point of view into line with 'common sense', which looks on sleep as a simple cessation of activity, a sort of negative state. However, the problem of sleep is not so simply resolved.

First of all, there are different levels of sleep, just as there are of wakefulness. During normal sleep, not all contacts with the outside world are broken. The best proof of this is the fact that certain signals which arrive from the outside during sleep are understood as such and are capable of awakening us. How such a filtering of sensations is possible during sleep is as yet imperfectly understood.

## *The mechanisms of sleep*

But these different levels of sleep do not simply represent different levels of passive cessation of activity of the reticular formation. Sleep also implies an active braking, an inhibition of the nervous system. While the idea of a 'sleep centre' has been abandoned, it is now known that several nervous structures exist which can exert powerful inhibitory influences on the nervous system and so can counterbalance the activating influence of the reticular formation and thus contribute to sleep.

There exists, in particular, a small region of the reticular formation just at its base, in the median region of the medulla. Stimulation of this region causes an extremely powerful inhibition of the muscles, as well as of the sympathetic nervous system, and of the electrical activity of the cerebral cortex. The activity of this inhibitory area of the reticular formation is normally dominated by that of its neighbour, the activating area, and its inhibitory potential is masked during wakefulness. But as soon as the 'tone' of the activating area is reduced, by whatever agent, then the activity of the inhibitory area is released. Diminution of facilitation and augmentation of inhibition are added to each other. When we are ready to sleep, we reduce our activity voluntarily and by lying down we reduce the inflow of sensory impulses concerned with maintaining, by reflex, the upright posture. We also try to reduce outside stimulation by taking advantage of the darkness of the night and of places that are relatively quiet. In this way, the sensory impulses to the reticular formation are greatly reduced, the tone diminishes, and as a result, the facilitating action which it exerts on our movements is reduced. Thus is set off a series of chain reactions which is completed by the intervention of the inhibitory area of the reticular formation, liberated by the start of the process and which precipitates it.

The intervention of these active mechanisms of inhibition is not always set off by this initial voluntary seeking for sleep. Sleep has a protective function which is essential for the organism and which eventually supervenes, whatever we do. It has been possible to study the effect of prolonged periods of wakefulness in dogs. At the end of these long spells without sleep, the animals fall into a state of deep sleep from which they cannot be awakened. If at this stage some cerebro-spinal fluid is taken from such an animal and injected into a normal dog, the latter will display an imperative need for sleep. This fact has led researchers to think that there are special toxins which are secreted by the organism when metabolic waste products begin to accumulate dangerously during the course of prolonged wakefulness, but their chemical nature is not yet known. Their function would be to set in motion a blocking of the mechanisms of vigilance and the positioning of the mechanisms of restoration. Without sleep it is possible that an accumulation of metabolic waste products would lead to the death of the organism.

Man, like the animals, normally takes his sleep at regular intervals, well before any real need for protective action makes itself felt. There must thus exist a sort of anticipatory mechanism which must have been acquired in the course of evolution and which is subject to a whole series of conditioning influences during ontogeny. The sleep of the newborn baby is polyphasic in contrast with the monophasic sleep of the adult, ie, in the baby one finds an alternation of short periods of sleep and wakefulness which occur irregularly during the day and night. Moreover, the distinction between sleep and wakefulness is not very clearly marked at this early stage, as has been shown by electroencephalographic studies on premature babies. In fact, such studies show no difference in pattern between sleep and wakefulness until eight months of foetal life. About a fortnight after the birth at full-term, this polyphasic rhythm tends to become simpler and little by little gives way to the monophasic form, which moreover comes to coincide with the nocturnal-diurnal rhythm. During this interval, a whole series of external compulsions and experiences acquired through conditioned reflexes will have intervened. Some scientists have put forward the theory that the nocturnal rhythm of sleep in the adult is associated with a daily cycle of variation in body temperature, which may itself be a reaction acquired through the physical and social environment.

We said at the beginning that behaviour has a dimension that can be described as intensity. Contemporary research has led to the discovery of facts of considerable importance for the understanding of this idea and has shown how nervous structures exercise a regulatory action on the level of vigilance. But sleep, which we used as a zero point in defining our scale of vigilance, does not confine itself to this dimension of intensity. Sleep is also a mode of behaviour and cannot be explained in terms of a single mechanism.

## Sleep and vigilance

*Although of an opposite nature, to all appearances, the slumber reflexes and the reactions of vigilance are dominated by the same part of the brain, called the 'reticular formation', and experiments carried out on animals have proved this. Thus the monkey in the lower photograph, crouching in an attacking position, will change its defence rictus into a yawn if the aggressive reaction it has started cannot be followed through to the full. (Photos Lod, the lower one taken in the laboratory of Professor Goustard, Laboratoire d'Évolution des Êtres organisés, Paris).*

# The visceral brain

*Hubert MAMO*

*One of the great accomplishments of modern neurophysiology is that of the discovery of the fundamental role played by the 'visceral brain' in regulating the behaviour of the individual in relation to his environment. The understanding of this cerebral structure, phylogenetically of great antiquity, now opens to neurologists, psychiatrists, and psychologists many new avenues of approach to the problems of epilepsy, as well as to those of the mechanisms of memory and dissociation of thought.*

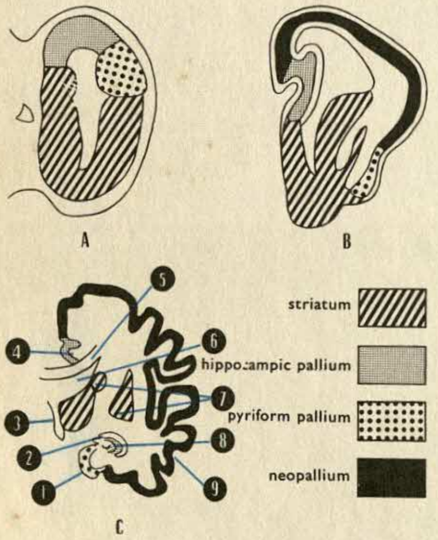

*Fig. 1. The evolution of the rhinencephalon as shown in cross-section.* (a) *fish: the rhinencephalon makes up the whole cortex.* (b) *marsupial: considerable development of the neocortex which pushes the archipallium inwards and the paleopallium downwards and outwards.* (c) *man: the archipallium is pushed in towards the corpus callosum and the paleopallium has come to lie in the innermost part of the lower face of the hemisphere. (After Gastaut and Lammers).*

'A man left home one morning to go to work. Twenty-four hours later he was found exhausted at the wheel of his car 150 miles away. He could remember nothing of what had occurred during this time, his last memory being of coming down the stairs at home. An electroencephalograph was taken of him in hospital, and this showed the existence of an epileptic focus in the temporal region of the brain.'

This patient had had an epileptic loss of memory, during which he was able to do everything needed for driving his car, such as avoiding obstacles and even obeying traffic lights. Two things, however, distinguished his behaviour from that of a normal person. The first was the absence of any purpose in his activity, the second was the lack of foresight, as shown by the failure to have his petrol tank filled up. In other words, the power of constructive thought and planning had been replaced by an automatic type of activity. More exact examination revealed that the lesion which was responsible lay in the rhinencephalic part of the brain.

'A man who had undergone a neurosurgical operation was found in the post-operative period to have a tremendous increase in appetite. This was marked not only by complete insatiability, but also by a total absence of discrimination in the choice of what he ate; he would even eat the container as well as the food, provided, of course, that it *could* be eaten! This patient had had a tumour removed from the temporal region touching on the rhinencephalon.'

These two clinical examples, chosen from a great number of a similar type, show the great importance of the 'visceral brain' in the behaviour of the individual in relation to his environment. The complexity of the functions of this structure has during the past half-century stimulated much work, both on the clinical side with observations of patients, and in animal experiments. In spite of this we are far from having a clear picture of the exact nature of the activity of this part of the brain.

## *The evolution of neurophysiology*

In 1878, Paul Broca published a paper which remains a landmark today. He described a region which he had delimited from the rest of the brain, situated on the internal surface of the cerebral hemispheres. He indicated its anatomical limits, calling it the 'main limbic lobe', often called today 'Broca's area'. The author justified this identification by the fact that this formation unites the greater part of the cerebral nervous structures constituting the 'old brain', and appears early in the evolutionary scale of vertebrates, thus forming, in a way, a common denominator of the brains of mammals.

The phylogenetic stability of this 'basal' brain contrasts with the rapid evolution of the 'recent' brain represented by the cerebral neocortex covering the surface of the hemispheres in higher vertebrates, the greatest development of which, in terms of cell numbers, is found in man.

Anatomical and phylogenetic unity suggests also a functional unity. The limbic lobe, which has extensive nervous connections with the olfactory organs and is largely developed in those animals which rely principally on their sense of smell, was therefore considered for a long time to be concerned only with the perception of smells and their integration in consciousness. It was thus often given the secondary name of rhinencephalon. In fact, this view was altogether too superficial, for it ignored the greater part of the functions of this structure. Physiologists soon noticed several contradictory pieces of evidence which could not be accounted for by this view of a purely olfactory function. For example, man has a very poorly developed sense of smell compared with most vertebrates, but the 'rhinencephalon' in man is proportionately richest in cells of all those in the animal kingdom. Also, certain other vertebrates without sense of smell show a considerable development of a part of the rhinencephalon. Parts of the structure can be removed experimentally without affecting the power to discriminate between different smells.

Thus it was logical to consider that this structure had several functions. The attention of physiologists was then attracted by the fact that most of the pathways of sensation seemed to make their way to the rhinencephalon and that this seemed to be in very close relation with other structures known to have an important role in integration, such as the hypothalamus.[1] Experiments in which parts were removed or stimulated finally convinced the research workers of the central role which this formation plays in the regulation of behaviour in relation to the external environment.

## *Some phylogenetic and anatomical conceptions*

The evolution of the neocortex in mammals had two effects on the arrangement of the primitive structures in the hemispheres. If we consider first a series of transverse sections of the brain at different points in the course of its phylogenetic transformation, we shall see that the neocortex in the course of its development comes to press back the older cortex, the archipallium and the paleopallium, away from the centre. These two latter formations come finally to line the internal surface of the hemisphere, while the neocortex covers the whole of the convex outer surface (fig. 1).

If we now study this morphological evolution in a longitudinal section, we see a considerable expansion of this new structure which forces the hemisphere, limited by the inextensibility of the cranial vault, to curve its posterior pole downwards and forwards. At the end of this manoeuvre the cerebral hemisphere appears to have rolled itself around a hilum represented by the corpus callosum and the central grey nuclei, which themselves form the upper part of the cerebral stem.

The mass of nerve tissue so disposed (fig. 2) then establishes close relations with both the underlying integrative formations, such as the hypothalamus and the reticular formation,[2] and also with the overlying cerebral cortex, in particular that of the temporal lobe. Thus in all phases of the behaviour of the individual, whether conscious or automatic, it is kept in touch with all the sensory events which are signalled by the peripheral receptors. This privileged position between the deeper formations of ancient origin and the superficial ones of recent evolution suggests the fundamental character and the complexity of its physiological effects.

## *The role of the visceral brain*

In brief outline we may distinguish two activities which are frequently interrelated: first, a specific activity of olfaction which is related to those functions centred on the oral cavity, and second, a non-specific activity of a more complex type on which depends the behaviour of the individual in relation to his environment.

The reception and integration of olfactory stimuli take place in the amygdaloid nucleus,[3] a structure situated in the base of the temporal lobe (fig. 2). Examples from the clinical field demonstrate the importance of this formation in the perception of smells. Infiltration by certain tumours or irritation by scarring may lead to the appearance of epileptic fits which are characterized by the sudden perception of a smell, usually disagreeable, which has no material cause. It is logical to connect feeding behaviour with the sense of smell, because although this behaviour is not specifically associated with the rhinencephalon, it has nevertheless close links with smell. We all know from personal experience how taste and smell can either stimulate or inhibit the appetite. This connection between smell and appetite was given force when experimental workers finally detected in the hypothalamus (where there is a centre concerned with satiety) impulses which had been originated by olfactory stimuli. In addition, certain lesions of the rhinencephalon are not only capable of leading to considerable quantitative deviations in appetite but also to qualitative changes, with the disappearance of discrimination between what is nutritious and what is not. The latter is more than a simple question of appetite; it is in fact a disorder of the instinct of self-preservation, since the patient is no longer able to choose the food that is necessary to maintain life.

It is perhaps going too far to adduce any connection between the sense of smell and sexual behaviour in man, but this is certainly

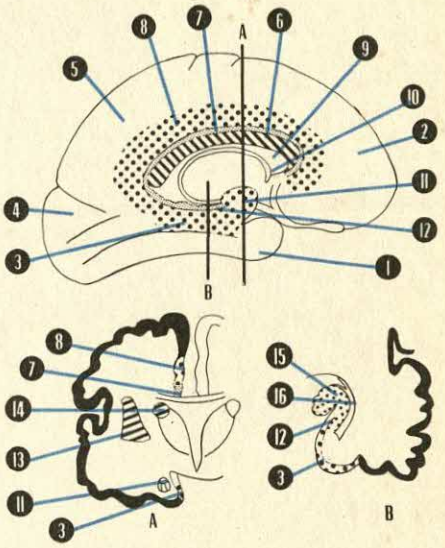

*Fig. 2. The rhinencephalon in man. Above, view of the internal face of the cerebral hemisphere. Below:* (a) *cross-section at the level of the line A.* (b) *cross-section at the level of the line B.* (*1*) *temporal lobe;* (*2*) *frontal lobe;* (*3*) *pyriform lobe;* (*4*) *occipital lobe;* (*5*) *parietal lobe;* (*6*) *corpus callosum;* (*7*) *remains of the hippocampus (archipallium);* (*8*) *lingual gyrus (cortex lying between the archipallium and the neopallium);* (*9*) *septum;* (*10*) *fornix;* (*11*) *amygdaloid nucleus of the rhinencephalon;* (*12*) *hippocampic fissure;* (*13*) *putamen (plus pallidum);* (*14*) *caudate nucleus;* (*15*) *hippocampus (Ammon's horn);* (*16*) *temporal horn of the lateral ventricle.*

(1) Hypothalamus: *a cerebral structure situated at the base of the brain at the level of the floor of the third ventricle.*

(2) Reticular formation: *a cellular network extending from the lower region of the medulla to the upper part of the brainstem. It plays a fundamental physiological role in the maintenance of vigilance.*

evident in many animals. The removal of the two temporal lobes of a monkey, crippling the deeper rhinencephalic structures, has led to a deviation in sexual behaviour marked by excessive sexuality and an absence of discrimination in the choice of partner. The monkey may choose for a partner an animal of a different species, one of the same sex, or even an inanimate object. The characteristics of this disorder in sexual behaviour are closely related to those of the deviations in alimentary behaviour, the hyperactivity engendered no longer being directed towards the preservation of the species, and constituting a retrogression of instinct.

This fundamental characteristic of the visceral brain has also been found in studies made on the behaviour of an animal after lesions have been induced in the amygdaloid nucleus or after the horn of Ammon[4] has been removed (fig. 2). Damage to these structures can cause considerable changes in reactions to the external environment. These changes may involve either excessive docility, with complete loss of all sense of danger, or excessive aggressiveness, producing the condition known to neurophysiologists as 'sham rage'. Electrical stimulation of the region of the amygdaloid nuclei has been successful in reproducing behaviour of attack or defence, ranging from the simple phenomenon of alarm to aggressive rage and an attack on the observer. Stimulation of the horn of Ammon has occasionally led to reactions of flight.

In human pathology, lesions of the hippocampus[5] have led to considerable changes in the character of the individual, resulting in sudden excesses of motiveless rage and fury, which have ceased when the source of irritation has been removed. The affective potentiality of the rhinencephalon and its role in the control of mood have led neurosurgeons to undertake localized resections of this region (cingulectomy) which reduce the conditions of irritability, aggressiveness and permanent psychomotive disturbance.

Damage in the rhinencephalon, particularly in the hippocampus, has been found to lead to marked effects on memory. Although memory is certainly a complex process, in recent years it has become possible to assign to it a certain anatomical basis. The most important research has been into the part played by certain basal nuclei known as the mamillary bodies.[6] Lesions of these bodies have been known to cause a state of confusion, with amnesia for recent events, and a tendency to replace memory by invention. More recently, attention has been drawn to the hippocampus, which seems to be concerned with the fixation of memories and the recall of recent events. It is logical to suggest that there exists a circuit of memory, bearing in mind the close anatomical connections of the hippocampus and the mamillary bodies. This circuit, however, by no means explains the whole subject of memory which, to be effective, must also possess a permanent temporal and spatial integration and have an intact affective background.

Structural damage in the rhinencephalon can also give rise to automatic movements which may come on suddenly and without warning from time to time. They may fall into one of two categories. In the first, the activities do not differ from normal ones, except that they are unexpected. The person breaks off whatever he may be doing or saying and starts doing something quite different, which leaves him confused when he suddenly returns to a normal state of consciousness. In other cases, activity is suddenly turned towards the search for some hypothetical object which the person tries to find, overturning everything within reach in his efforts.

Both experimenters and clinicians have come to agree that these different modes of behaviour are often accompanied by emotional reactions which can come about according to two different affective ranges. Animals, in most cases, seem to feel disturbed and anxious, as is shown by a motor disturbance and plaintive cries; in the case of man there is often a feeling of extreme anguish and sometimes a sensation of impending death. Occasionally, on the other hand, reactions of pleasure have been noted during the course of stimulation of the amygdaloid nucleus; a cat, for instance, will begin to purr and rub against the legs of the experimenter. Another such example has been seen in the behaviour of animals that have had stimulating electrodes inserted permanently into the septal region,[7] and are able to close the electrical circuit of excitation. When a current is passed through these electrodes, the animal shows all the marks of intense pleasure, so much so that it is willing to work for long hours in order to gain this recompense, which it values as much as food. Similarly, in human cases, certain forms of epilepsy associated with lesions of the rhinencephalon have been characterized by feelings of euphoria and intense pleasure, which may be so appreciated by the patient that he is unwilling to have treatment to end the attacks.

*Opposite right:*
*It is the visceral brain which controls emotional reactions such as those of this young monkey: deprived of its mother, it clings in preference to any other object to a piece of fur which recalls the maternal breast. (Photo Lod; taken in the laboratory of Professor Goustard, Laboratoire d'Évolution des Êtres organisés, Paris).*

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(3) Amygdaloid nucleus: *part of the rhinencephalon formed by a group of nuclei situated in the depths of the temporal lobe (in the region of the uncus).*

(4) Ammon's horn: *part of the hippocampus forming the infero-internal wall of the temporal horn of the lateral ventricle.*

(5) Hippocampus: *a structure situated in the centre of the limbic formation made up of two distinct convolutions, Ammon's horn and the gyrus dentatus.*

(6) Mamillary bodies: *hypothalamic formations situated on the external face of the floor of the third ventricle.*

(7) Septal area: *a formation situated above the olfactory gyrus and under the anterior part of the corpus callosum. It is made up of the gyrus subcallosus and the septum.*

## *The unity and the place of the rhinencephalon*

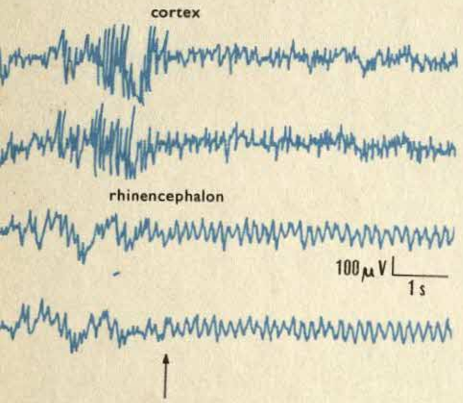

*Fig. 3. Modification of the cortical rhythms (upper plottings) and the hippocampic rhythms (lower plottings) under the stimulation of a painful stimulus (arrow). It will be noted that before the stimulation the electro-encephalogram is 'synchronized' in the cortex and 'desynchronized' in the rhinencephalon. After the stimulus the phenomenon is immediately reversed.*

The multiplicity and the complexity of the manifestations arising in the rhinencephalon, touching as they do on memory, alimentary functions, sexuality, smell, socio-emotional behaviour, and the idea of the preservation of the individual and the species, present research workers and observers with many problems.

First, is it a question of a structure possessing only an anatomical and phylogenetic meaning, or of its possessing a physiological one? The multiplicity of activities which we have described obliges us to reject the idea of a single function and to put forward the possibility that the rhinencephalon acts as a functional link in the process of integrating the different 'happenings', both internal and external, thus modifying the general attitude of the individual. Except for its connection with smell, the rhinencephalon has no intrinsic function of its own, ie, one that cannot be activated by the stimulation of a structure. The basic 'centres' for the different elements of behaviour are situated in other parts of the 'old' brain, in particular in the area of the hypothalamus and mesencephalon. The role of the rhinencephalon must therefore be one of control, so that damage to it leads to a distortion of behaviour, with loss of orientation and purpose. It therefore appears as the higher integration centre of the 'old' brain, not as the creator of 'attitudes'.

Secondly, what are the similarities and what are the differences in the organization and functioning of the 'old' rhinencephalic brain and the 'recent' cortical brain? On the purely electro-physiological plane, two fundamental contrasts appear: the electrical reaction of 'awareness', set off by some sensory stimulus, is totally different in each of these two structures. The changes in the electrical rhythms in the cortex consist of a considerable increase in the frequency, and a decrease of the amplitude, of the waves (reactions of desynchronization). In the rhinencephalon, on the other hand, there is an increase in the amplitude and a decrease in the pre-existing electrical activity (reaction of synchronization) (fig. 3). Perhaps there is a possibility, based on the opposite character of the reaction to the same outside events, that these two formations are antagonistic and that in particular the 'old' brain may have an inhibitory role in regard to the 'recent' brain. This hypothesis is attractive, but has not so far received any experimental confirmation.

A second difference in electro-physiological activity concerns the organization of the neuronal circuits in the two formations. It is known that a sensory stimulus will produce an electric potential at a precise point on the cerebral cortex. The localization of the cortex is a function of the place of origin and of the nature of the original stimulus. Physiologists have, in fact, been able to draw up maps of the sensory and motor areas. In the case of the rhinencephalon, however, a receptor electrode placed anywhere in this structure (apart from the purely olfactory area) will pick up a potential, whatever and wherever the sensory stimulus may be. We are therefore led to affirm the existence of a convergence of stimuli of all kinds and from all points, by identical groups of cells. This second differential character enables us to say that if the cortex is made up of a mosaic of specific representations of an analytical character, the rhinencephalon appears as a system for synthesis, having a generalized cellular activity and setting off a 'mass' reaction in the individual.

These fundamental differences between the formations lead to certain reflections on phylogeny and psychiatry. In man, the 'recent' brain which has come to cover the 'old' brain has in no way provided a functional replacement for the latter, but, on the contrary, has enriched the possibilities of the individual by giving him the means of exact analysis and so facilitating his approach to the outside world. One can picture the cerebral organization in the form of two concentric spheres, the internal one representing the 'old' brain and the external one the 'recent' brain. Normally, these two spheres function synchronously, the emotional and affective behaviour corresponding to the habit dictated by information from outside, and this in relation to the intellect of the individual. The appearance of a lack of synchronism in the movement of the two spheres will produce alarming effects on the psychic behaviour of the individual which will no longer adapt itself to the information. This disturbance of the affective connections with the external world might then be the origin of true psychoses with dissociation of the personality, such as is found in schizophrenia.

Thus the role of the rhinencephalon, which was a mystery until some thirty years ago, is essential to the organization of the important cerebral functions, influencing at the same time both the oldest and the most recent of the structures of the central nervous system.

# Regulation and control of arterial blood pressure

*Corneille HEYMANS*

*The circulation of the blood is essentially the result of the differences in pressure which prevail within the different parts of the circulatory system. The left ventricle contracts and propels the arterial blood under pressure into the vascular system; the blood then passes through the large arteries into the arterioles, the capillaries, the venules, and the veins. This blood finally returns to the right side of the heart as venous blood, and the right ventricle propels it through the lungs. Here it is aerated and returns as arterial blood to the left side of the heart, to circulate again.*

In an adult man the average pressure in the main arteries (as, for example, the carotids) is about 90 mm of mercury. In the medium-sized arteries (eg, the radial) it is about 85 mm of mercury. In the capillaries it falls to 10–30 mm; in the small veins it is about 9 mm; in the inferior vena cava about 3 mm; and in the large veins of the neck it varies from 0 to 8 mm (fig. 1). Each contraction of the heart (called systole) leads to a slight rise in the arterial blood pressure (systolic or maximum pressure), while in the phase of rest and refilling of the heart (diastole) there is a slight fall (diastolic or minimum pressure).

## Arterial pressure

The pressure of the arterial blood in the main arteries, or the general arterial pressure, is regulated by the work done by the heart, the tonus and elasticity of the main arteries, and the resistance and capacity of the peripheral vessels, ie, the arterioles, capillaries and veins. Let us examine the role played by these different factors in the regulation of arterial pressure.

## The work done by the heart

The work done by the heart is basically determined by the cardiac output, ie, the quantity of blood which is expelled by the ventricles at each contraction, or in each minute. The cardiac output depends in turn on (1) the amount of blood which returns to the heart from the venous system, and (2) the energy and frequency of the contractions themselves. If the other factors remain constant, a fall in cardiac output will lead to a fall in the arterial pressure, while a rise in output will lead to a rise in pressure.

(1) *The return of venous blood to the heart.*

This depends particularly on the following factors:

(*a*) The contractions of the skeletal muscles expel the blood which they contain and propel it towards the heart. The veins are furnished with valves which prevent the return of blood towards the muscles when these relax.

(*b*) The respiratory movements in the course of inspiration draw the venous blood towards the chest cavity, and thus towards the heart.

(*c*) The capillary blood pressure is slightly positive, and this helps the passage of blood into the veins in which the pressure is lower. This capillary pressure itself depends on the afferent arterial pressure and on the diameter of the capillaries.

(*d*) The tonus (diameter) of the capillaries: when the tonus is low and the capil-

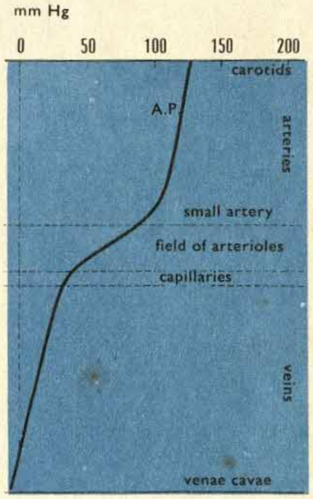

*Fig. 1. Mean blood pressure, in millimetres of mercury, in the various regions of the main circulation.*

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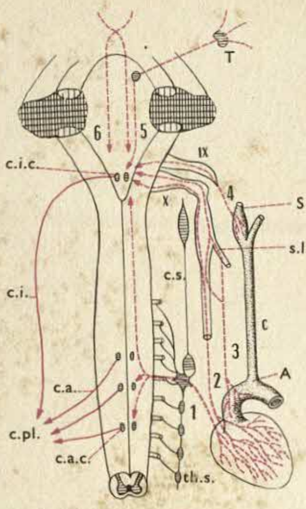


*Fig. 2. Diagram of the connections of the cardiac centres. On the right the dotted lines represent the afferent (centripetal) tracts which transmit the sensory impressions to the cardio-inhibitory centre (c.i.c.) and the cardio-accelerator centre (c.a.c.). On the left the continuous lines show the efferent (centrifugal) tracts, both inhibiting (c.i.) and accelerating (c.a.), which converge on the cardiac plexus (c.pl.). At the junction of the thoracic (th.s.) and cervical (c.s.) sympathetic chains lies the stellate ganglion through which pass both the accelerator efferent fibres and the sensory fibres coming from the heart (1). Other sensory fibres from the heart (2) and from the arch of the aorta (A) reach the inhibitory centre via the vagus nerve (X). (3) The depressor nerve, coming from the aorta, branches to enter the vagus and also the superior laryngeal nerve (s.l.). At the bifurcation of the carotid artery (c) one can see the dilation of the first part of the internal carotid, called the carotid sinus (S). (4) The carotid sinus nerve sends impulses originating in the carotid sinus to the cardio-inhibitory centre, via the glosso-pharyngeal nerve (IX). (5) Sensory impulses come in via the trigeminal nerve (T). (6) Impulses emanate from the brain. (After E. Hédon).*

laries dilate, their capacity is increased and they retain a larger volume of blood. Thus there is less blood available to return through the veins to the heart. The capillary tonus depends especially on chemical factors, such as the amount of carbon dioxide, oxygen, and the various metabolites contained in the blood. Histamine causes intense capillary dilatation and so reduces the return of blood to the heart, often to a marked degree.

(*e*) The venous pressure, ie, the pressure of the blood in the small and large veins, depends on the general arterial pressure, the peripheral resistance of the arterioles and capillaries, the work done by the heart, the tonus of the walls of the veins themselves, and finally the extent of the respiratory movements. The walls of both small and large veins have a vaso-motor innervation, the vaso-constrictory or vaso-dilatory action of which is controlled from the vaso-motor centre in the central nervous system. Chemical factors may influence such activities, either through central or peripheral action.

(*f*) Changes in the blood volume. Venous return to the heart is reduced when the blood volume falls, as, for example, after a haemorrhage, and is increased if the blood volume is raised, as by a transfusion.

(2) *The energy of the systolic contraction of the heart.*

This depends particularly on:

(*a*) The initial, pre-systolic length of the cardiac muscle fibres. In principle, the more the muscle fibres are lengthened at the time of the pre-systolic phase of the diastole, the more vigorously will they contract during systole (Starling's Law). This pre-systolic lengthening is dependent especially on the venous return, ie, the amount of venous blood which flows into the heart during diastole, and which thus regulates the filling and distension of the cavities of the heart during this period.

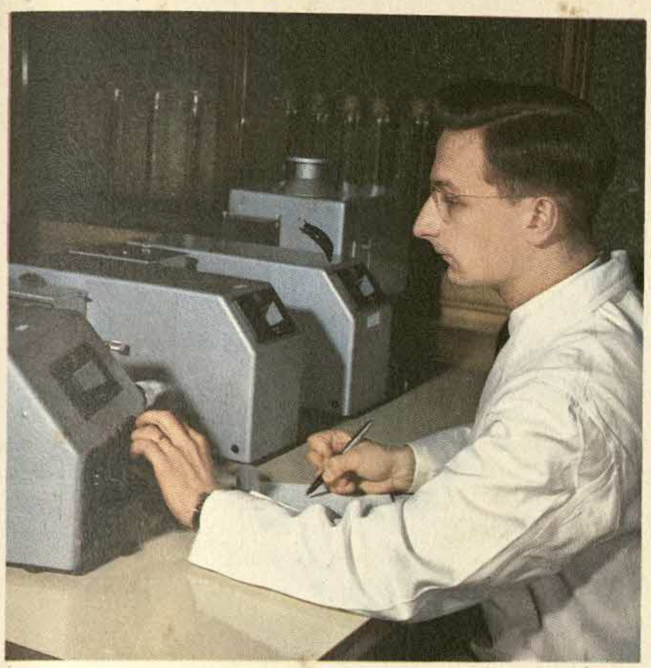
(*b*) The frequency of the heartbeat, which influences the cardiac output both directly and indirectly, since it acts on the force of the systolic contraction, the diastolic filling of the heart, and the cardiac output. The heart has within itself the stimulant of its rhythmic contractile activity. A heart which has been isolated and then perfused will continue to beat in an automatic manner. Various agents produce by direct action on the heart either a speeding-up or a slowing-down of the rhythm, ie, either a tachycardia or a bradycardia. Among those producing bradycardia we may note: cold, deprivation of oxygen; potassium, acetylcholine, digitalis, quinine, etc. Factors which cause a speeding-up of an isolated heart include rise in temperature, adrenalin, and numerous drugs.

Extrinsic variations in the frequency of the heartbeat are produced in the intact animal or human being through impulses from the central nervous system. The nerves which regulate the frequency of the heartbeat and its strength, as well as the cardiac output, belong to the autonomic nervous system. They include the sympathetic nerves which accelerate the heartbeat, and the cholinergic nerves, in particular the vagus nerve, which slow the rhythm and reduce the vigour of the contraction (fig. 2). The centres for these nerves are situated in the brain-stem and upper part of the spinal cord. One can consider several methods by which the cardio-regulatory centres may work; by direct action from the centre, through reflex action, and through action at the level of the various elements of the cardio-regulatory nerves themselves. It should be noted too that the cardio-regulatory centres are also affected by other vegetative centres and by the higher psychic and motor centres.

## *The main arteries*

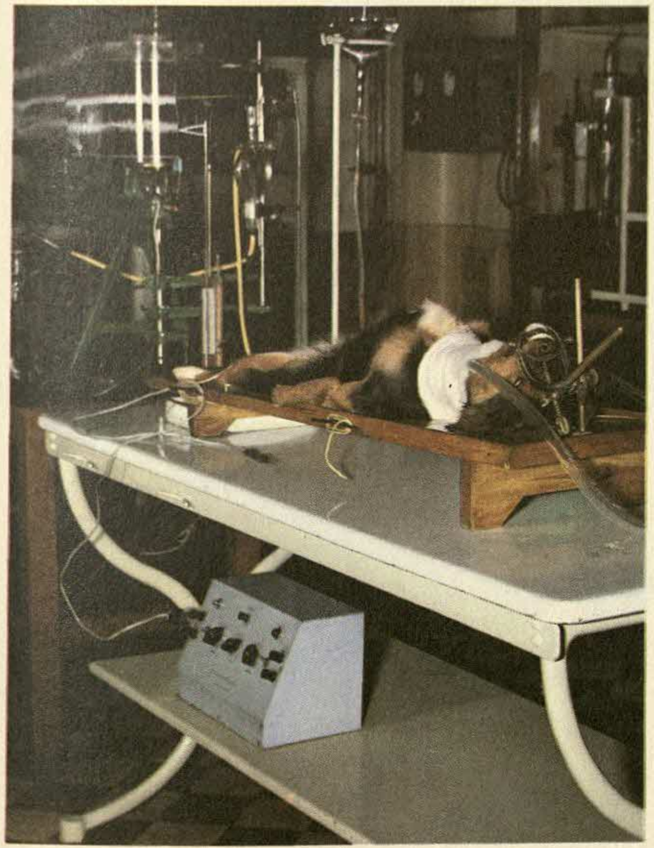
The main arteries assist the work of the heart in maintaining the arterial blood pressure at its normal level, particularly during the period of rest, or diastole, of the cardiac cycle. The walls of the main arteries are in a certain state of contraction or tonus and have a certain degree of elasticity.

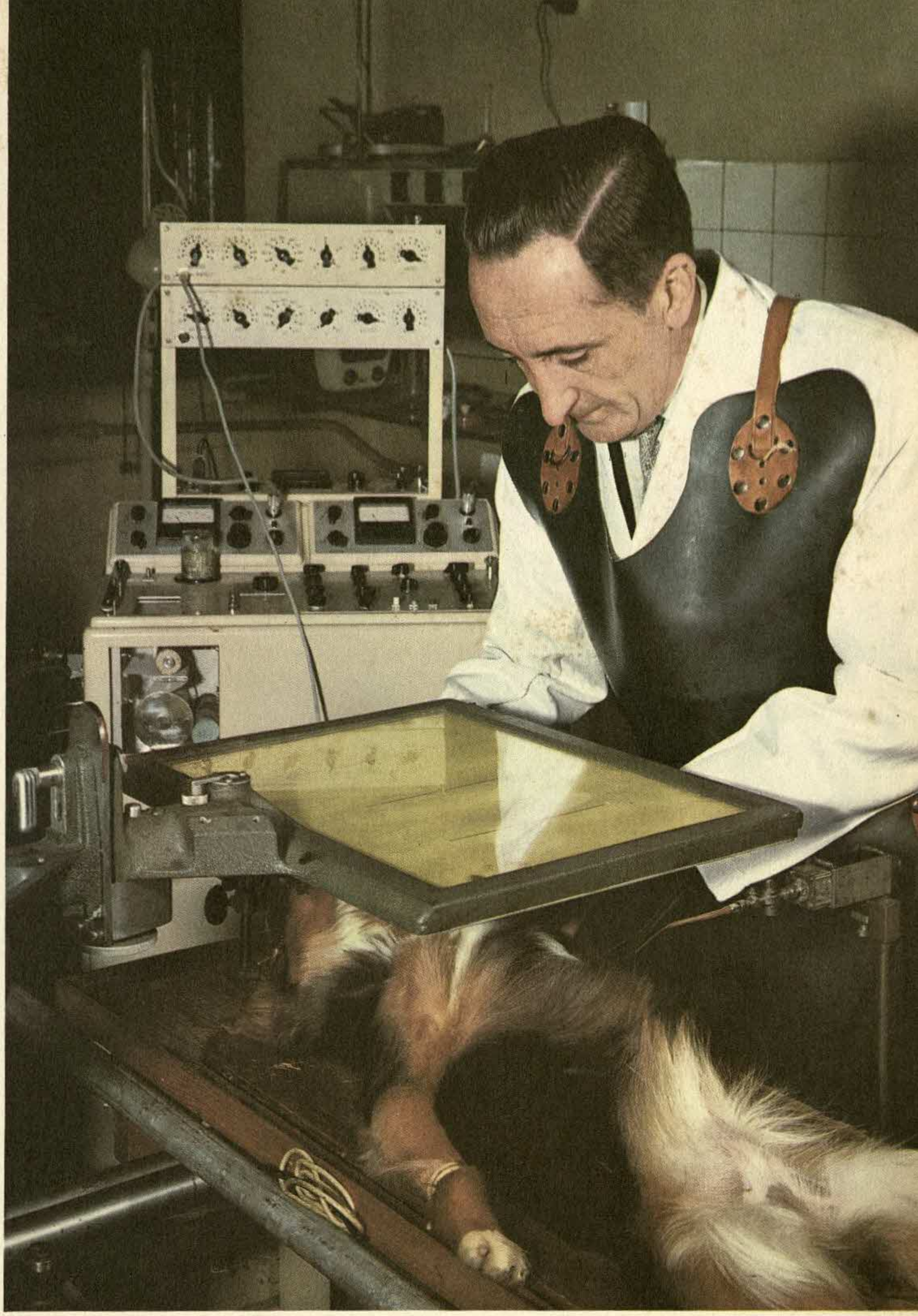
(1) The tonus of the main arteries depends chiefly on the intrinsic properties of the arterial walls and in particular on the degree of contraction of the smooth muscle fibres found in them. This tonus is affected by local physical and chemical influences. Thus the pressure within the artery itself influences the tonus; a rise in pressure leads to an increase in tonus. Adrenalin and the extract of the posterior lobe of the pituitary (vasopressin) both cause contraction of the main arteries, while lack of oxygen and excess of carbon dioxide cause them to dilate. Besides these alterations in tonus, which are usually slow, the arterial walls also show contractions and relaxations of a more rapid nature which are active and rhythmic and could be called true arterial pulsations. By contracting after the wave of systolic pressure the arterial walls contribute to the propulsion of the blood towards the periphery and help to maintain the pressure during diastole. Thus they contribute to the maintenance and regulation of the systolic, diastolic and mean arterial pressure.



*The use of the Zeiss spectrophotometer for measuring substances in the blood by spectrophotometric and photometric methods.*

*The catheter is in place and the experimental animal is anaesthetized on the operating table. A smoked drum, visible in the top left corner, shows the trace of the activity of the heart and the arterial blood pressure.*





*The experimenter is introducing a tube (catheter) into the heart of the animal in order to register the intracardiac and intravascular pressures. He is following the movement of the catheter on a fluorescent screen.*

*In the control of the functioning of an organism, the measurement of arterial pressure is one of the simplest and at the same time the most accurate means of investigation. The apparatus shown here is that used by Professor Heymans for his remarkable work on the regulation of blood pressure. (Photo Lod).*

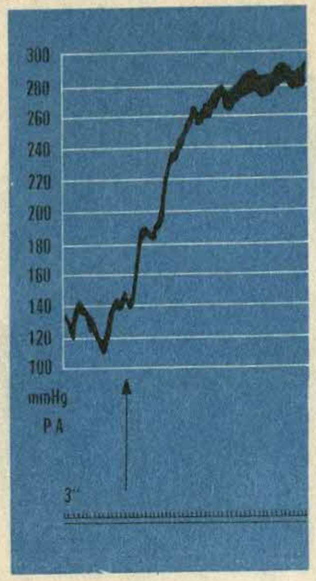
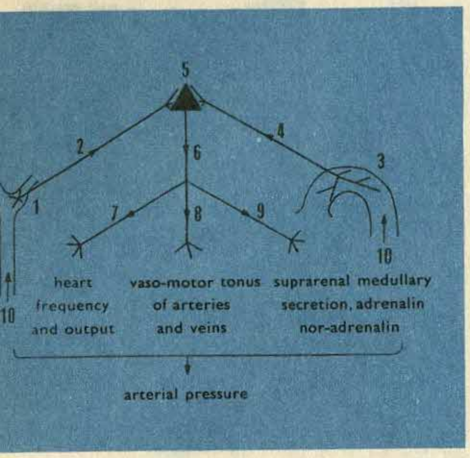


*Fig. 3. Arterial pressure, in millimetres of mercury, recorded from the femoral artery of a dog. The arrow indicates sectioning of the aortic depressor nerves and of the carotid sinus nerves. The normal arterial pressure of 10 mm Hg rises to 300 mm Hg (hypertension).*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heart frequency and output
vaso-motor tonus of arteries and veins
suprarenal medullary secretion, adrenalin nor-adrenalin
arterial pressure

*Fig. 4. Reflex control (homeostasis) of arterial pressure. (1) Carotid sinus; (2) nerve of the carotid sinus; (3) aortic arch; (4) aortic or depressor nerve; (5) cardio-vascular centres; (6) cardio-regulatory and vaso-motor nerves; (7) cardiac vagus and sympathetic nerve branches; (8) vaso-motor nerves; (9) nerves controlling suprarenal medullary secretion; (10) arterial pressure in the pressure-sensitive zones of the aortic arch and carotid sinus.*

(2) The elasticity of the main arteries is a physico-biological property which depends mainly on the connective tissue of the walls. This elastic property supplements the effects of muscular tonus on the maintenance of the blood pressure and the circulation.

## The peripheral vascular resistance

The resistance offered by the arterioles and capillaries to the flow of blood is preponderant among the various mechanisms controlling the arterial pressure. Peripheral vascular resistance is largely provoked, maintained and controlled by the degree of contraction (vaso-constriction) or relaxation (vaso-dilatation) of the arterioles, and to a lesser extent of the capillaries. Under normal physiological conditions most of the arterioles are constantly under the influence of nervous impulses which lead to constriction, a general vaso-constrictor tonus. For this reason, if an organ is deprived of its vaso-motor innervation, the arterioles at once dilate vigorously.

The vaso-motor tonus of the arterioles, ie, their degree of constriction or dilatation, is also under the influence of various local neurogenic and chemical activities. Thus carbon dioxide, lack of oxygen, and an acid pH all cause direct dilatation of the arterioles, while adrenalin and nor-adrenalin cause constriction. The arterial neurogenic vaso-constrictory tonus is largely of encephalo-bulbar origin and arises only to a slight degree from the medulla. Thus, if the cord is cut in the cervical region, there is an intense general vaso-dilatation and therefore a considerable fall in blood pressure. The activity of these vaso-motor centres is influenced by both direct and reflex mechanisms. The centrifugal pathways which connect the vaso-constrictory centres to the peripheral vessels are located in the sympathetic part of the autonomic nervous system.

These sympathetic or adrenergic vaso-motor nerves can be stimulated at the level of their ganglionic synapses, or at their peripheral termination on the vessels, or even in the post-synaptic regions. Certain organs and tissues have also a cholinergic vaso-dilating innervation, the centres for which are situated in the central nervous system, especially in the brain-stem.

The peripheral vascular resistance is also affected by a hormonal mechanism, that is, through the secretion of adrenalin and nor-adrenalin by the suprarenal medulla. These hormones thus exert a humoral activity of vaso-motor type on the vasculature. Adrenalin and nor-adrenalin are vaso-constrictors which act also in a positive manner on the heart, influencing the frequency and the vigour of its contractions and so affecting the cardiac output. The secretion of the suprarenal medulla is itself under the control of the sympathetic innervation of the suprarenals. Certain agents exert either a direct or an indirect influence on the activity and the secretion of the suprarenal medulla.

## Mechanisms that regulate the arterial blood pressure

Ever since the existence of an arterial blood pressure was discovered and measured, physiologists have been interested in the mechanisms which regulate it. They were struck by the fact that the pressure is maintained within very narrow limits in spite of changes in the various factors which affect it. It was thus necessary from the start to assume that regulatory mechanisms exist. In 1836, Astley Cooper observed that occlusion of the common carotid arteries, an action which leads to a fall in the pressure in the arteries of the brain and head generally, provokes a rise in the general arterial pressure and an acceleration of the heartbeat. When the common carotids were freed, the pressure regained its normal value, as did the rate of the heartbeat. These observations were confirmed by Magendie, among others, in 1838.

Experiments carried out by various physiologists between 1877 and 1926 showed that if the pressure was raised in the carotid arteries and the cerebral circulation, there was a fall in the general arterial pressure and a slowing of the heartbeat, while a reduction in carotid and cerebral pressure led to reverse effects. These experimental observations were looked upon as a demonstration of an automatic regulation or homeostasis of the arterial pressure of direct central origin. Thus the idea of a sensitivity and reactivity of the cardio-vascular nervous centres to variations in the arterial pressure became one of the tenets of physiology.

Nevertheless, in 1900, Pagano and Siciliano had already observed that although the occlusion and the release of the common carotid arteries were followed by the changes in arterial pressure and heartbeat already outlined, no such effects were found if the arteries leading from the common carotids, ie, the internal and external carotid arteries, were occluded and then released. These physiologists therefore concluded that the central cardiovascular centres were not directly sensitive to changes in the arterial pressure, but reacted in an indirect, reflex manner to nervous impulses from special pressure-sensitive receptors, which they postulated as present in the common carotid arteries. Other physiologists, however, took no notice of the observations of Pagano and Siciliano, which were in any case contradicted by Kaufmann in 1912 and by Kisch and Sakai in 1923. But further experiments from 1924 onwards, carried out particularly in the laboratories of Hering, Koch and Heymans, showed that the bifurcation of the common carotid artery, called the carotid sinus,[1] is provided with receptors which are sensitive to changes in the arterial pressure. When the pressure in the carotid sinus falls, the presso- or baro-receptors in this region set off compensatory reflexes from the nerve centres controlling general arterial pressure, reactions characterized especially by an accelerated heartbeat, an increase in cardiac output and peripheral vascular resistance, and an activation of the suprarenal medullary secretion. These compensatory reflexes bring about a rise in the general arterial pressure. When there is a rise in arterial pressure in the region of the carotid sinuses, their pressure receptors give rise to reflex compensatory reactions leading to a fall in pressure.

These experiments also showed that the nervous centres which are concerned with the regulation of the blood pressure are in fact not directly sensitive to changes in pressure. Thus the classic idea of homeostasis and the regulation of general arterial pressure by a central direct mechanism is false, and the new idea of reflex homeostasis through the intermediary of the pressure receptors in the carotid sinuses has taken its place.

## *The system of depressor nerves*

As early as 1866, Cyon and Ludwig had shown that the stimulation of the distal part of a nerve in the neck could cause slowing of the heartbeat and a reflex lowering of the blood pressure. According to these scientists, the terminations of this nerve, which they called the depressor nerve, were situated in the heart and were sensitive to changes in the intracardiac pressure. Later work by various scientists showed, however, that the pressure receptors of the depressor nerve were situated principally in the arch of the aorta, forming a mechanism parallel with that of the nerves of the carotid sinuses and controlling, with these, the reflex homeostasis of the general arterial pressure.

The work of Hering, Koch and Heymans showed also that the nerves of the carotid sinuses and the aortic depressor nerves with their receptors are inhibitory nerves as well as reflex restrictor nerves. If they are removed, there is an acute, followed by a chronic, rise in the blood pressure: a hypertension. Both these nerves are therefore permanent depressors of the arterial pressure. Fig. 4 shows diagrammatically the mechanisms of this reflex homeostasis.

How does the arterial pressure act on the pressure receptors of the carotid sinuses and the arch of the aorta? Histologists have shown that these receptors are situated in the arterial walls at a certain distance from the lumen of the vessel (fig. 5). Experiments carried out in our laboratory show that these pressure receptors in both sites react in fact to the variations in the intramural tension in the vessel wall. Normally, this tension is regulated by the pressure in the artery and particularly by the resistance which the wall offers to the distension which the pressure would cause. Thus the biological condition of the walls of the arteries which are sensitive to pressure plays a fundamental role in the reflex regulation of the blood pressure. These physiological facts obviously open new pathways towards the understanding of pathological hypertension.

Others have demonstrated the presence of pressure receptors in other parts of the arterial and venous systems. Pressure receptors occur, for example, in the venae cavae, the pulmonary veins, the heart, the pulmonary circulation, the mesenteric arteries, and the common carotid arteries. These are not, however, concerned in the homeostasis of the general arterial pressure, but seem rather to play a role in certain mechanisms concerned with regulating the frequency of the heartbeat and the cardiac output, and also in regulating the distribution of the blood in different parts of the circulation.

Finally, nerve endings sensitive to chemical, physiological and pharmacological materials, ie, chemo-receptors, have been identified in the glomi in the area of the aorta and carotid arteries. These chemo-receptors (fig. 6) play an important role, particularly in the reflex physiological regulation and the pharmacological reactions of the respiratory centre. Certain reflexes of a chemo-sensitive origin also play a part in the mechanisms of the physiological or pharmacological adaptation of the circulation of the blood, both general and local.

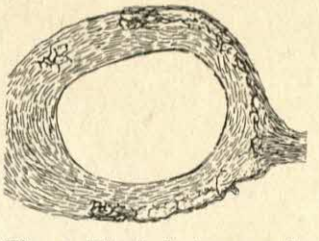

*Fig. 5. Histological preparation of a pressure-sensitive artery of the carotid sinus. Pressure-sensitive nerve endings are seen in the arterial wall, with their nerve fibres.*

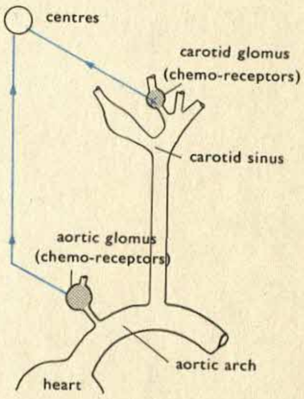

*Fig. 6. Diagram of the chemo-sensitive aortic and carotid glomi with their nerve connections.*

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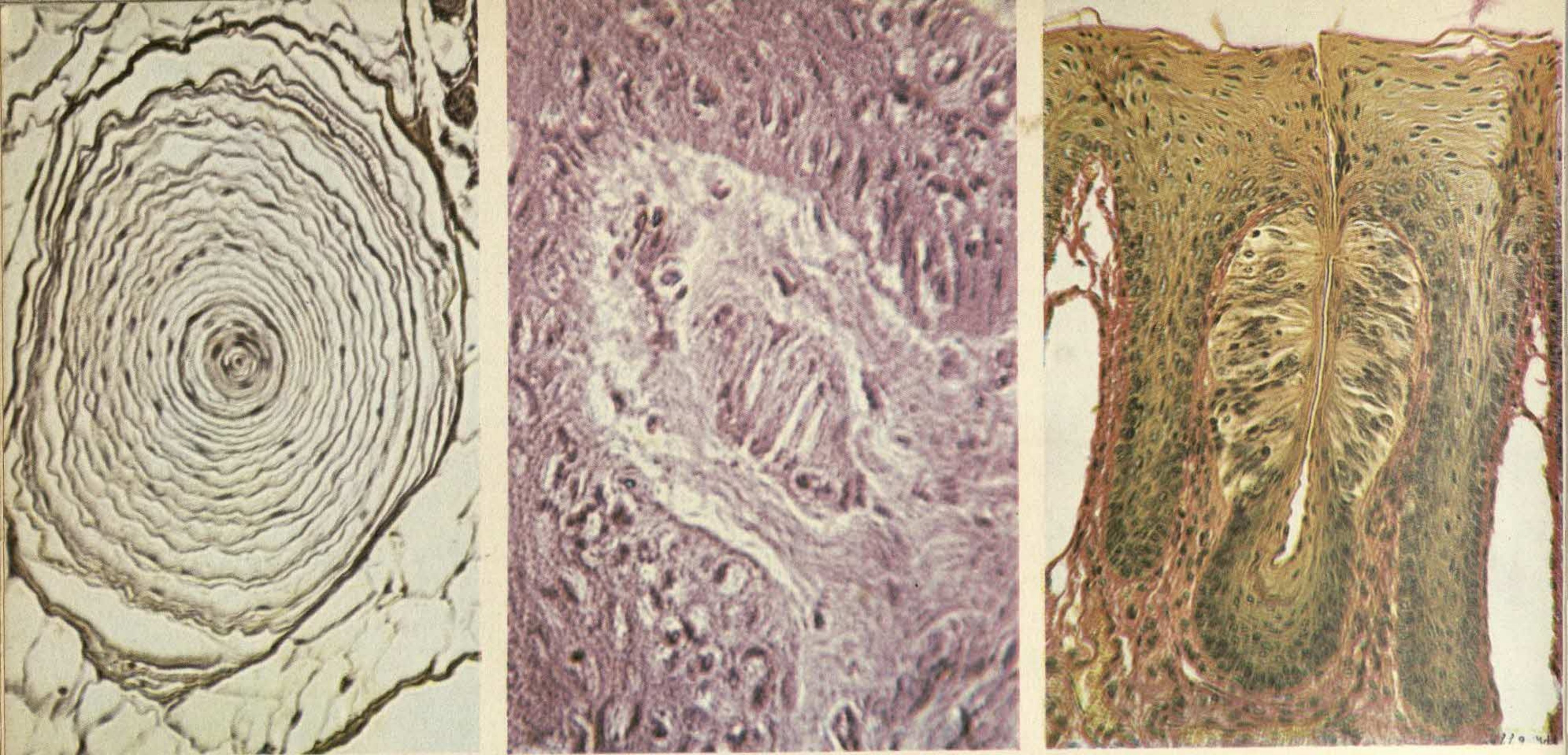
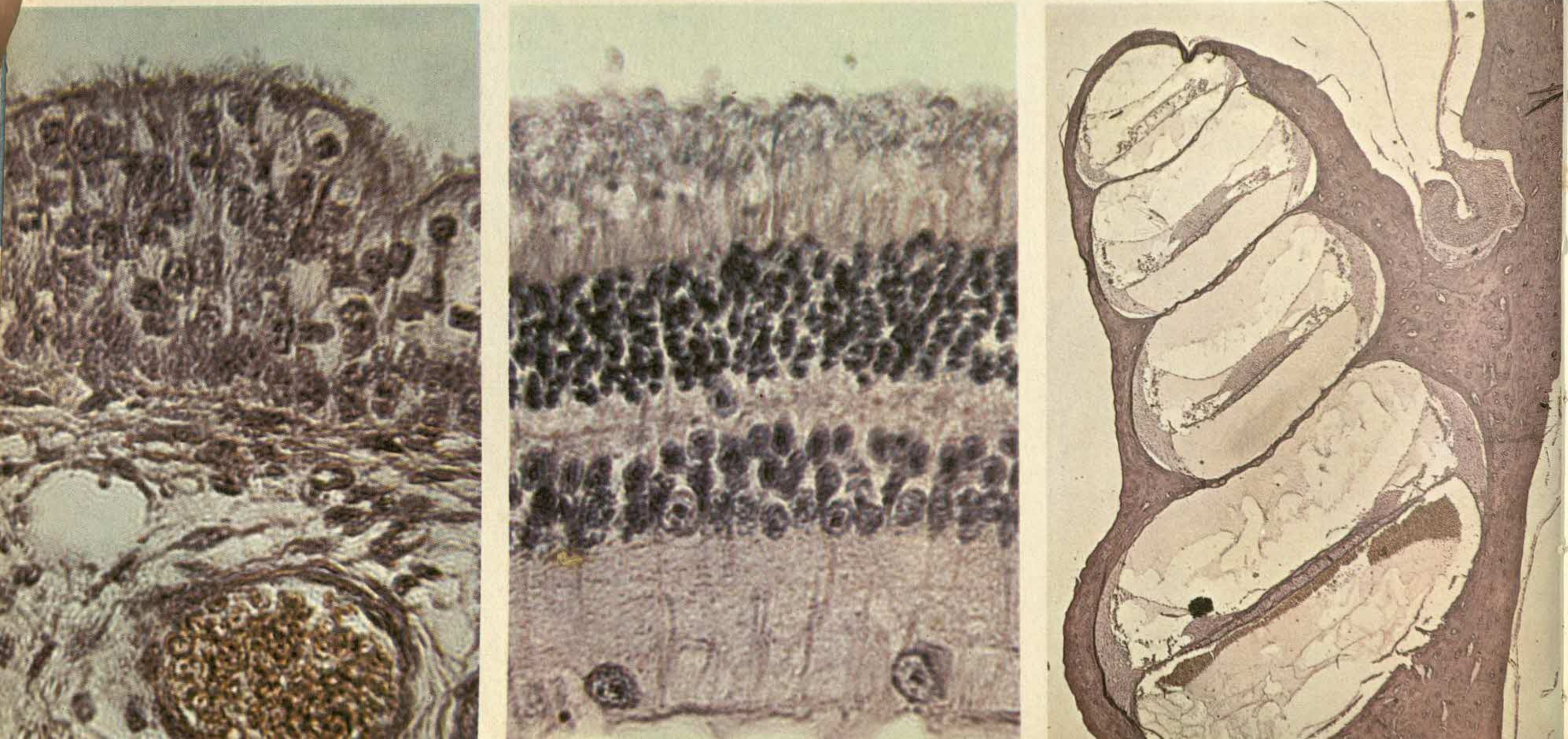
[1] Carotid sinus: *a slight swelling situated at the bifurcation of the common carotid artery into the internal and external carotids.*

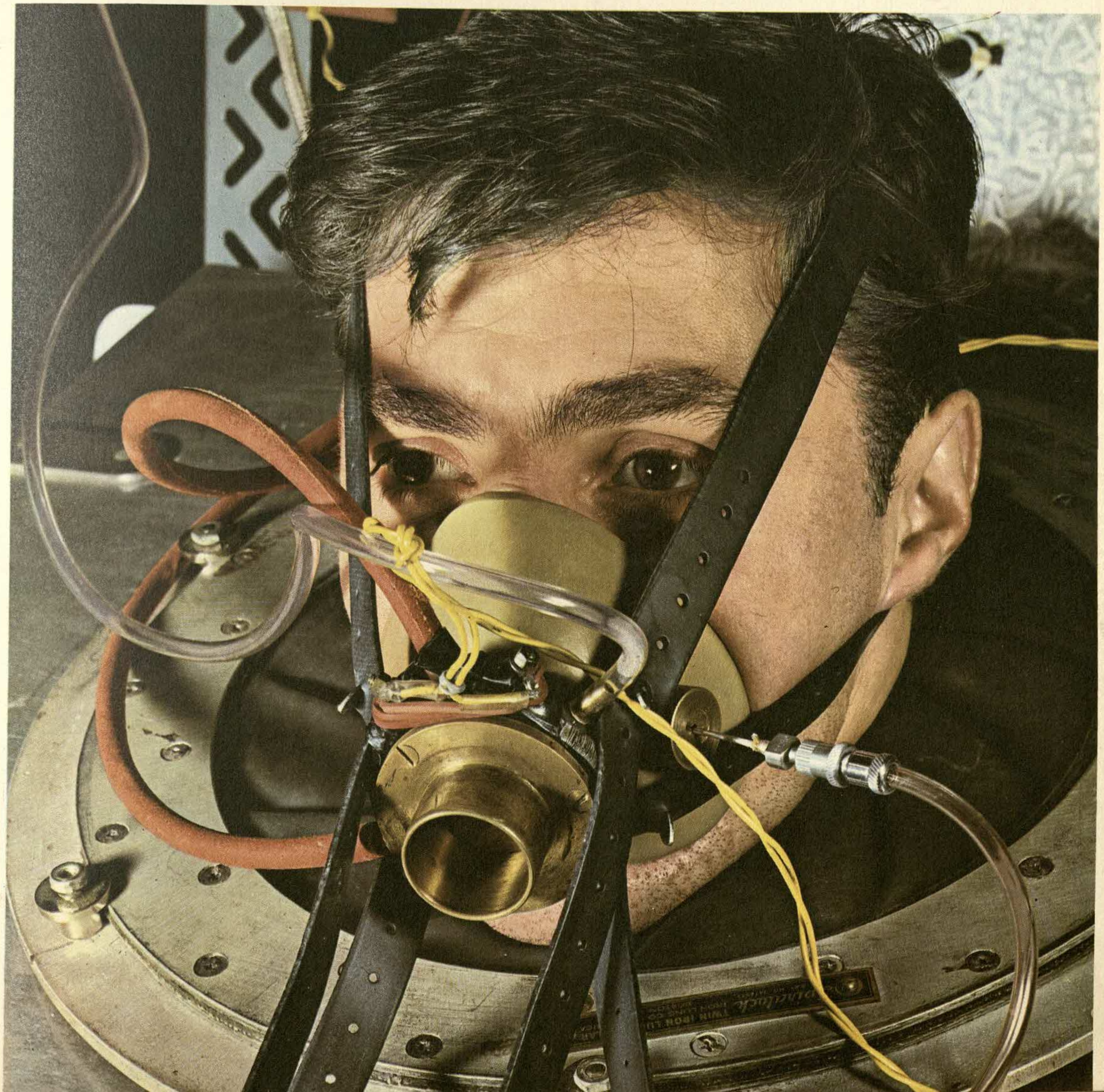


*It is through the sense organs that we make our contact with the outside world. Sight, hearing, taste, smell and touch are traditionally looked upon as the five most important senses, if not the only ones. Above, from left to right, we see: a Pacini corpuscle, a Meissner corpuscle, and a taste bud. Below, a section of olfactory mucosa, a section of the retina, and a section of the cochlea. The normal functioning of the five senses is an important test of whether the human machine is working properly. From this stems the present interest in experiments which seek to find out at what limits of pressure and temperature these organs transmit incorrect information (right-hand page). (Photos Lod. The first two above were taken in the laboratory of Professor MacLeod, Faculty of Sciences, Paris. The third one above was taken in the laboratory of Professor Verne).*



PART FIVE

# *Links with the outside world*



# The sensory message

*Yngve ZOTTERMAN*

*The essential element in every communication is a signal. The nervous receptors, each according to its special function, transform light, sound, heat, cold, smell, taste, pressure, etc, into corresponding messages which are coded into signals. It was a great surprise to many when it was first definitely established that the nervous system uses only one signal, the nerve impulse, which is transmitted at rates varying from 0·1 metre to 160 metres per second, depending upon the special properties of the nerve fibres.*

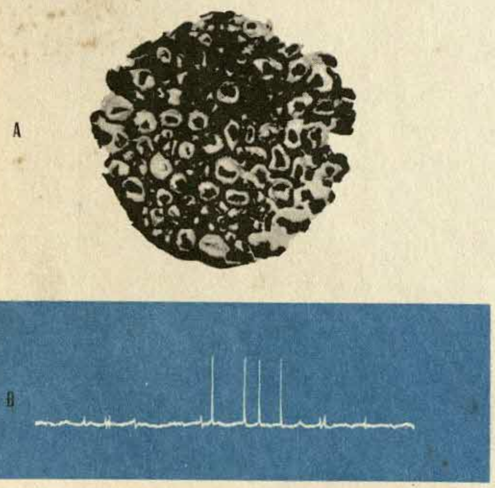


*Fig. 1. A: microphotograph of a lingual nerve preparation, enlarged 940 times (the diameter of the larger fibres is 10 microns). B: recording obtained with this nerve, showing the relation between amplitudes of potentials produced by cold (exposure of the tongue) and by touching the tongue with a brush (see the four spikes).*

Only a few decades ago our knowledge of the functioning of the sensory nerves was in the main the outcome of experiments on man or animals, the reaction of the subject to sensory stimuli serving to indicate the underlying processes in the nervous system. Earlier investigations of the function of sense organs were thus mainly carried out by means of psychological methods. Whatever views we have on the relation of physical and psychic events, there is a very unsatisfactory gap between two such events as the dropping of burning wax on a finger and the painful sensation experienced. In part, the gap is obviously made up of events occurring in the sensory nerves and brain. Psychological methods cannot by themselves tell us anything about these processes. Fortunately, this gap has in recent years been partially filled by modern electro-physiological studies.

In 1925, Lord Adrian, using an electronic amplifier in conjunction with rapidly recording oscillographs, recorded for the first time impulses from sensory nerve fibres in the sciatic nerve of the frog, nerve fibres which respond to stretching of the muscles. The sciatic nerve contains a mass of afferent fibres sending impulses from muscle spindles. These sensory mechanisms are highly important in the co-ordination of our movements. The records taken at that time showed an irregular series of impulses obviously deriving from very many nerve fibres. It was like listening in to the signals in a large telegraph cable where there is a simultaneous signalling traffic in 50 lines or more. It was not possible to understand what was signalled in the separate fibres. For that purpose it was necessary to find a nerve-muscle preparation which contained only one or a few functioning sensory fibres. The choice fell on a small thin muscle from the chest of the frog—the sternocutaneous muscle which takes origin from the body wall and is inserted into the skin. This was dissected in such a way that a small piece of skin was left attached to the free upper end, so as to stretch the muscle by weights hanging from a thread tied to the skin. The nerve to this muscle contains from 15 to 25 nerve fibres. Leads were taken from this nerve while the muscle was stretched, and we obtained a series of fairly large spikes at an irregular frequency. We thus understood that this muscle contained more than the one muscle spindle which we had hoped for. But before we abandoned the sternocutaneous muscle, we made an attempt to reduce the number of stretch receptors by cutting off small strips of muscle on the medial side, in the hope that we should be left with a piece of muscle containing only one end-organ.

This method was successful. At last we succeeded in obtaining a preparation which in response to stretching gave a regular volley of spikes. Since two or more sensory nerve fibres could scarcely give rise to a single regular series of impulses, the preparation must have contained only one end-organ, and this end-organ gave a regular series of discharges in response to a constant stimulus. With such a preparation it was then possible to make a whole series of fundamental observations. We found that the more we loaded, ie, stretched, the muscle, the more closely the impulses followed each other. The frequency thus varied with the strength of the stimulus as well as with the rate of stimulation, ie, the quicker the muscle was loaded, the higher was the rate of impulse discharge. It could also be shown that within a wide range the size of the single action potential is independent of the intensity of the stimulus applied to the receptors. A stronger stimulus induces only a change in the frequency with which the receptor discharges impulses through the nerve fibre. In this way the final proof was obtained of the 'all or none' principle which Keith Lucas and Lord Adrian had previously advanced as applying to the nerves. The principle could now be extended to the sensory nerve fibres as well.

A hundred years earlier, Johannes Müller had formulated his law of specific energies, ie, that whatever the method of stimulation of a sense organ, the resulting sensation will always be of the same character as when it is stimulated by the natural stimulus.

After the discovery by Magnus Blix (1882) of warm and cold spots in the skin and his demonstration that electrical stimulation of a cold spot elicited a cold sensation, Müller's law was given a wider formulation by stating that different sensory modalities are mediated by specific nerve fibres.

## *Taste*

We all learn early in life that there are four basic tastes: sweet, acid, bitter and salt. In 1891, Öhrwall demonstrated that some taste buds reacted only to salt and acid but not to sweet and bitter, and vice versa. From these observations it was generally assumed that the four qualities of taste were subserved by specific receptors which discharged into specific nerve fibres, and that these specific fibres signalled to specific cells in the cortex of the brain. Recent electrophysiological studies of the impulse traffic in the taste nerves have in general confirmed this conception. The response of single taste-nerve fibres in different animals—cats, dogs and monkeys—have revealed that the taste fibres seem to a certain extent to be specific, but also that this specificity, at least in mammals, is not always quite strict. Thus it has been observed that strong acid solutions applied to the tongue do not stimulate only specific 'acid fibres' but also salt fibres. The salty taste would thus be distinguished from acid taste only by the absence of impulses in the specific acid fibres. However, in the monkey, quite a few salt fibres were found that did not respond to acid, and it may be possible that the specificity of taste fibres, or rather their end-organ, is even more specific in man in comparison with other mammals. Recent investigations have revealed, not only very many species differences but also individual variations in taste. It was observed that the cat's taste nerve entirely lacked taste fibres responding to sweet-tasting solutions like sugar and saccharine, in contrast to animals like the rat, the dog and the pig, which have a large number of fibres subserving sweet taste. In contrast to those of the monkey, the sweet-taste fibres of the dog do not respond to saccharine. Further, it was discovered that some animals like the cat, the dog, the pig and the monkey possess taste fibres which respond to the application of pure water on the tongue, while the rat lacked this positive response. This finding, however, revived the old problem as to whether man was equipped with specific taste organs for water.

It was recently found possible to record the electrical response from the chorda tympani nerve in man. It is a freak of nature that all the taste nerve fibres from the anterior two-thirds of the tongue separate from the other sensory fibres of the lingual nerve to form a special small nerve, the chorda tympani, which after passing through its own bony canal to the tympanic cavity winds round the ear-drum before it joins up with the facial nerve. During ear operations, the chorda tympani nerve is thus easily exposed. When we listened in to the electrical response from this nerve, it became evident that the nerve responded positively to the application of salt, sweet, bitter and acid solutions on the tongue. The application of water to the human tongue, however, was followed by a negative response, in that water abolished the spontaneous activity of the taste fibres, particularly the salt fibres. The specific effect of water on taste in man can thus be looked upon as being of the same nature as that of blackness upon vision. This is in interesting contrast to the monkey, in which water taste elicits a comparatively strong positive response.

**Fibre type response in the monkey**

| Stimulus | 'Salt' fibre | 'Acid' fibre | 'Sweet' fibre | 'Bitter' fibre | Sensation evoked |
|---|---|---|---|---|---|
| NaCl (0·05 M) | + | O | O | O | Salt |
| HCl (pH 2·5) | + | + | O | O | Sour |
| Sucrose (0·1 M) | O | O | + | O | Sweet |
| Quinine | O | O | O | + | Bitter |

Table salt (NaCl) is the only salt that gives a pure salt taste. All other salts are savoured with more or less marked mixed

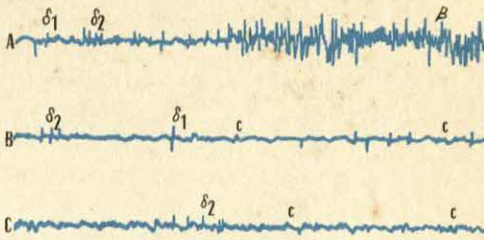


*Fig. 2. A: a sharp blow is given with a wooden point. B: the same, recording three seconds later. C: flash lasting 1/50 sec. (reading from right to left).*

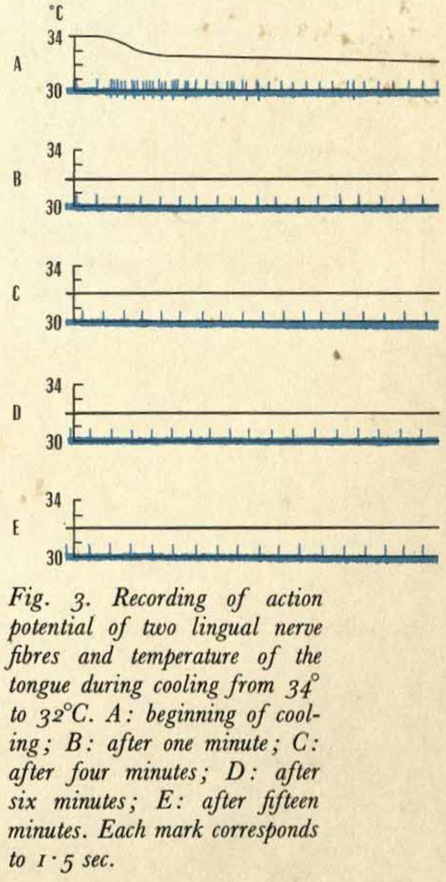


*Fig. 3. Recording of action potential of two lingual nerve fibres and temperature of the tongue during cooling from 34° to 32°C. A: beginning of cooling; B: after one minute; C: after four minutes; D: after six minutes; E: after fifteen minutes. Each mark corresponds to 1·5 sec.*

tastes, acid or bitter. Different sapid substances interact to give composite sensations of taste, and the interaction takes place not in the qualitatively different peripheral sense organs, but somewhere in the brain, in a manner analogous to the perception of a mixture of colours. The sense of taste, however, never fuses different savours as sight fuses colours, and it is always possible to distinguish the ingredients of mixed tastes more or less accurately.

## *Cutaneous sensations*

The skin as a sensory organ has long been a puzzle to investigators because the same stimulus—a light touch, for example—evokes not only very different sensations when applied to different parts of the skin, but the sensation produced may also vary from time to time. Further, a very light mechanical stimulus may evoke quite a powerful reflex—a fly walking on the skin, for example, produces a scratch reflex, while a much stronger mechanical stimulus, a finger firmly pressed against the skin, does not elicit any reflex at all.[1] A skin stimulus may also evoke a sensation of cold or warmth when it respectively cools or heats the surface of the skin. Behind all such reactions there is the function of the dense system of nerve fibres which innervate the skin. An examination of the cutaneous nerves reveals that they consist of numerous nerve fibres of which about 20 per cent are myelinated and 80 per cent unmyelinated, the former of a diameter of 15 to 1·5μ, conducting at rates of from 90 to 10 m/sec, the unmyelinated fibres being less than 1μ in diameter and conducting at rates below 1·5 m/sec.

Ever since Blix (1882) discovered that cold and warmth could be elicited only from distinct points of the skin, anatomists have tried in vain to find the specific structures of end-organs subserving the thermal sensations. The skin contains a few encapsulated nerve endings and nets of nerve fibres around the hair follicles, but the majority of fibres end up as naked fibrils, some of them running up even between the most superficial epithelial cells.

It has now become evident that the structure responsible for the receptor specificity, ie, its transducing activity, is not attached to any specific encapsulation of the nerve ending, but is most likely dependent on differences in the molecular structure of the naked nerve-ending filaments which are not revealed by the microscope. It has been suggested that the capsule of a sensory end-organ as, for example, the onion-shaped Pacinian corpuscle, may play another role, ie, of protecting the naked nerve ending when it is particularly exposed (below tendons, and at the tip of a woodpecker's beak). Peeling off the outer membranes of the Pacinian corpuscle, leaving only the inner core with its enclosed nerve ending, does not change the responsiveness of the end-organ.

Experiments on single sensory fibres, carried out not only on animals but also on humans, have shown that there are in the skin highly specific end-organs which respond very selectively to mechanical stimulation, when the stimulus produces a visible deformation of the surface of the skin. Further it has been proved that cold and warmth are mediated by specific nerve fibres. Besides these specific fibres, however, there are numerous myelinated sensory fibres which respond to pressure as well as to cooling: this would explain the old observation that a cold object is felt to be heavier than another of the same weight and size which does not cool the skin.

## *Sensations of pain*

Should pain be considered a special sense, subserved by specific nerve endings and conveyed by specific afferent fibres? The old intensity theory—that pain can be produced by stimulation of any sensory fibres when the strength of the stimulation exceeds a certain level of intensity, has had its supporters until today. As the strength of the excitation process produced by the stimulus in the end-organ is signalled by the sensory nerve fibre in a frequency code only, it should imply that pain would result from the signalling of any nerve fibre whenever the impulse traffic reached a certain level. This is definitely not the case. Mechanical and thermal stimuli which have been demonstrated to produce maximum frequency in their respective nerve fibres do not elicit any pain reactions. Further, painful stimulation of the skin, like pinching, pricking, heating the skin above 45°C, etc, elicit, besides the response of specific mechanoceptive and thermal nerve fibres, an additional excitation of other nerve fibres which are active only when pain is produced. Pain is conveyed by specific nerve fibres which are stimulated specifically by painful stimulation: pinching, pricking, extreme temperatures, etc. The pain fibres are found to be widely distributed over the whole fibre range, with the exception of the largest medullated fibres, which apparently are not nociceptive.[2] Pain and thermal sensation are conveyed by

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(1) *This may explain why itching, for example, when the nasal mucosa is tickled with a wad of cotton, causes a stronger reaction than vigorous mechanical pressure. Itching arises from the stimulation of very fine superficial skin fibres. We know that these often follow the same path as pain fibres in the central nervous system. When they are sectioned (cordotomy), there is no longer any itching, although the senses of touch and pressure are preserved. Strong cutaneous sensations thus totally disappear after an operation which cuts the fibres sending a considerable number of impulses towards the reticular system. It is more than fifty years since psychologists first suggested that itching was caused by specialized fibres. This hypothesis has yet to be verified. There is no doubt, however, that the sensation usually defined as tactile is not caused by a simple mechanism. It must not be forgotten that sensory structures of the skin have taken millions of years to evolve.*

(2) Nociceptive: *causing pain.*

medullated as well as non-medullated fibres conducting at speeds from 40 to 0·5 m/sec.

In summing up, it can be said that touch and pressure, cold and warmth, as well as pain, are transmitted by specific nerve fibres to the central nervous system. These specific nerve fibres are distributed fairly widely over the whole range of fibre sizes.

## *The nerve fibre paths*

After entering the spinal cord or the brain stem, the sensory fibres segregate into two separate tracts. One of these, containing the specific fibres for touch and pressure and for muscle sense, sends its fibres directly up in the posterior column; while the other specific thermal and nociceptive fibres immediately relay and transmit their messages through fibres on the opposite side of the cord into a tract running up to the thalamus. The severance of this latter tract in the spinal cord, an operation called cordotomy, produces a complete loss of pain and thermal sensations on the opposite side of the body below the level of the lesion. Concerning the further ascent of the cutaneous sensory pathways from the thalamus to the cortex, it is well known that the third relay neurone in the somaesthetic pathways conveying touch, pressure and muscle sense, runs to the post-central gyrus of the parietal lobe. The thermal pathways most probably project also into the cerebral cortex; at least they do so as far as the tongue is concerned.

Records from single cells in sensory fields of the cortex have shown that the signalling pattern of the sensory end-organ may often be preserved as high up as the cortical level, in spite of the fact that the impulse volley passes at least two relay stations on its way. But besides using these sensory pathways which ascend directly to the cerebral cortex, the sensory messages are sent into that part of the brain stem called the reticular system, which controls, among other activities, the state of being awake. Recent research in this field has shown that different sensory messages exert different influences upon the state of vigilance, or, in other words, different stimuli have a different capacity for arousing. In this way noxious stimuli are particularly apt to produce vigilance because of an abundant inflow into the reticular formation which in its turn arouses the cortex.

## *The mechanism of transmission*

At each relay station in the sensory pathways the numerous nerve connections may also cause an interaction or integration of the sensory message; it may be increased or diminished in strength, or completely blocked, ie, inhibited because of interfering messages. The higher this interference occurs, the greater the degree of integration.

We can thus picture diagrammatically the mechanism for sensory communication in man and animals in the following way.

Information about changes in the physical and chemical environment of the organism is transmitted to the central nervous system through nerve fibres which constitute independent channels. Such changes (stimuli) produce in the sensory end-organ a receptor potential (generator potential) which, when a certain intensity is attained, discharges the nerve fibre. The intensity of the stimulus will thus be transformed into an impulse-frequency code in which each signal, the propagated nerve impulse, is of equal intensity, quite independently of the strength of stimulation. Within the central nervous system, these volleys of impulses will again be transformed into DC potentials at each relay station or will modify the DC potential of other cells in a positive (excitatory) or negative (inhibitory) direction, and the resulting synaptic potential will, if it attains a certain critical value, in its turn produce a volley of impulses to the next station. Thus we see how, within the nervous system, the initial receptor response is coded into volleys of a simple signal, the nerve impulse, which arrives at each relay station, where it is integrated into the synaptic potential. This in its turn is transformed into a train of impulses, and so on.

In the receptor, as well as at each relay station in the nervous system, there thus occurs an intensity-frequency transformation which corresponds to what is called pulse frequency modulation (PFM). If the nerve fibre did not function according to the all-or-none principle, then different intensities could as well be communicated by varying the strength of the individual signal, the nerve impulse (amplitude modulation). That would imply that the slightest interference with the nerve impulse during its propagation in the nerve fibre would lead to a change in the strength of the sensory message, corresponding to the fading which occurs with amplitude-modulated radio transmissions. It is amusing to find that the principle of pulse frequency modulation, fairly recently introduced in radio technique, has been the mode of transmission within the nervous system for as long as living beings with a nervous system have existed.

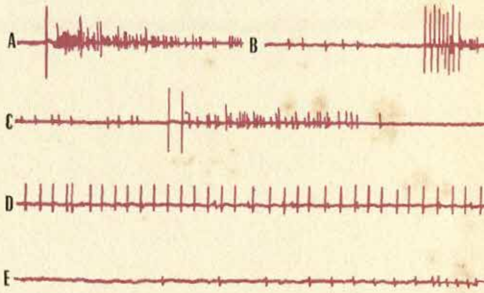


*Fig. 4. Afferent spike potentials emitted by different nerve fibres from a small section of a cat's lingual nerve under the effect of different stimulations of the tongue. A: a drop of water falling on to the tongue at a temperature of 14°C. B: a slightly stronger stimulus causes a visible distortion of the curve. C: a drop of water at 80°C. D: effect produced by the application of a point to the tongue. E: the surface of the tongue is sprayed with warm water (60°C). (From Y. Zotterman,* Specific Action Potentials in the Lingual Nerve of the Cat. *Skand. Arch. f. Physiol. 75, 105, 1936).*

# Photochemistry of vision

*W. A. H. RUSHTON*

*All that we know about the world outside us is derived from information collected by the nerve endings at the surface of our bodies. The most primitive of these respond to contact—mechanical or chemical—the sense of touch or of taste. But in the evolutionary struggle for existence great rewards are offered to those with advanced information, and but few species have been able to survive without the advantage of some kind of sight.*

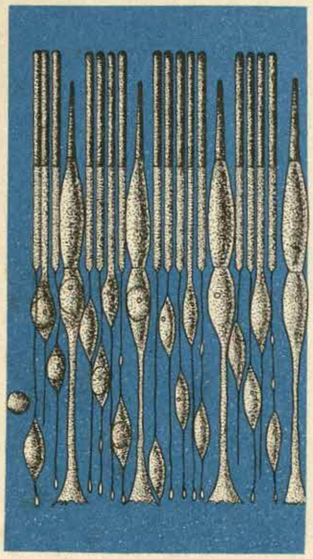


*Fig. 1. Rods and cones in the retina of man (after Schultze, 1866).*

Time and again in the course of evolution, nature has brought off a superb trick. We know how to touch, how are we to learn to see? By means of a lens, we form an image upon the retina. This is a private replica of the luminous world around us, and by 'feeling' this image we may 'touch' the stars. But how can we feel something so intangible as an optical image? It is light which forms the image, so light must do whatever is done when the image is felt, and what light does to matter is an atomic event.

In the same way that matter which seems so solid is in reality composed of countless atoms, so light which seems so steady is composed of a shower of energy atoms called 'quanta', and the starting point of vision is when these quanta of light are caught and their energy used to stimulate nerves. Now, any chemical substance which catches light quanta is called a pigment, so the retina must contain a suitable pigment.

The kind of pigment that first comes to mind is what we employ to colour objects—the paints and dyes, but these are not at all suitable to form the starting point of vision. For our paints must not fade in the sun or undergo any other chemical change. They must turn the light they catch gently into warmth without the violence of chemical disruption. But such gentle treatment will never irritate a nerve. What is needed for that is a sudden chemical breakdown, such as underlies the blackening of a photographic film. That kind of chemical change was first seen in the retina in 1876 by Boll.

It is easy to repeat Boll's observation. A frog kept overnight in the dark is brought into a photographic dark room, and by light of the safe lamp it is killed and the eye removed. The retina is dissected out and placed upon a white plate and then brought out into daylight. At first it is seen to be bright rose-red in colour, but as we look, the colour fades away to a pale lemon-yellow, and this bleaching is faster, the stronger the light. Thus the red pigment *rhodopsin* exhibits just such a change with light as might make it suitable to be the starting point of the visual process. But before we can say that it actually *is* the starting point, we must enquire something about the minute structure of the retina and where in it rhodopsin is to be found.

If under the microscope we examine the place where in the living eye the photographic image is formed, we find that the surface is composed of a mosaic of special cells called rods and cones. In the same way that the picture in a mosaic cannot exhibit detail finer than the little stones which compose it, so the detail which our eyes can resolve is limited by the fineness of the retinal mosaic of rods and cones. This, of course, is very fine indeed. The round image of the full moon only occupies about 0·02 square mm of retinal surface, but it covers 700 rods and cones.

We may ask what is the difference between the rods and the cones. First, as their names indicate, rods are cylindrical, and cones are pointed, so they are distinct in their appearance, as may be seen from fig. 1; moreover, in their functions a very interesting fact was discovered by Schultze (1866) from the comparative study of very many animals. For those animals which have few rods in their eyes go to roost or to ground at twilight, whereas those with very few cones come out at night. It is evident that cones are daylight receptors and rods are twilight receptors. Our eyes contain twenty rods for each cone, so we seem to be fitted for night life. However, we have developed a very special feature in our retinal structure which has allowed us to make the best of both worlds.

A fair proportion of the five million cones we do possess is clumped together in the very centre of the retina, to the complete exclusion of rods. This *fovea centralis* is the most precious part of our retina, for with it we read, recognize and do most of the things which we consider important in our visual lives. And our brain is developed to analyze in detail the information from this little fovea and to organize our eye movements, so that by darting here and there it may scan the whole world around us, like a bee in a garden, pausing to suck at the choicest flowers.

Now, the photosensitive chemical, rhodopsin, may be seen to be contained by the rods, not the cones, so if the quanta caught by rhodopsin are used for vision at all, it will be for rod vision—for the colourless and shadowy scene of a landscape lit by the half moon. But how can we tell whether or not rhodopsin *is* the pigment which catches the quanta by means of which we see? There is a very critical test. Rhodopsin does not catch light of all wave-lengths equally well. As may be seen from fig. 2, the quanta best caught have a wave-length of 500 mμ, while wave-lengths greater than 600 mμ are hardly absorbed at all. Clearly, quanta which are not absorbed cannot be seen, so that we should expect various wave-lengths of light to be seen in proportion to the ease with which they are absorbed. Put technically, the absorption curve should coincide with the visibility curve. The twilight visbility curve is shown by the circles in fig. 2 and the agreement with the absorption spectrum is so good over the whole range of visible wave-lengths that there can be no doubt that rhodopsin indeed catches the quanta which the eye uses for twilight vision.

## *Dark-adaptation*

It is a familiar experience that when we go from a brilliantly lit house into a moonlit garden or dark lecture room, at first we are nearly blind, but soon can see much better—a process which continues for about half an hour and is called 'dark-adaptation'. Hecht, about forty years ago, suggested that since in strong light rhodopsin is bleached away, and since in the dark the pigment is restored (in the living eye), the phenomenon of dark-adaptation might reasonably be ascribed to the regeneration of rhodopsin which had previously been bleached. This suggestion has seemed so plausible and has been so often repeated that it has found its way into the text books and journals without clear realization that the theory has never been supported by evidence. The difficulty has been to measure in comparable circumstances the two quantities which the theory claims are related. In animals, the time course of regeneration of rhodopsin may be determined by the laborious and exacting techniques of extraction from the eyes of dead animals, but it is hard to measure their visual threshold during adaptation. With living man, on the other hand, it is easy to determine the visual thresholds, but only in the last few years has a technique been developed by which rhodopsin may be measured as it regenerates after exposure to a bright light.

Fig. 3 shows a set of accurately determined curves made by Hecht and his colleagues over twenty years ago. After two minutes of exposure to bright or very bright lights, of retinal illuminations indicated, the subject remained in the dark and measured the least intensity of a flashing light which was just visible. This is plotted vertically upon a logarithmic scale. It is seen that from the first moment improvement begins, the curve falling very rapidly at first, then more slowly, and after thirty minutes there is not much further change. The eye is then fully dark-adapted. Most of the curves have two branches, the first of these being due to the cones, for this alone appears upon the rod-free fovea and flashes are seen in their proper colour. The second branch is due to rods, for the sensation is colourless, the spectral sensitivity corresponds to the absorption of rhodopsin and this branch is absent from the fovea. These curves, then, can be interpreted as follows: cones are

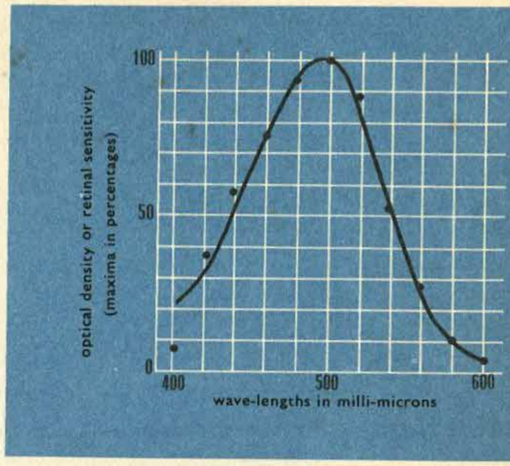


*Fig. 2. Absorption spectrum of rhodopsin. Points represent twilight vision (Crawford; after Crescitelli and Dartnall,* Nature, *1953).*

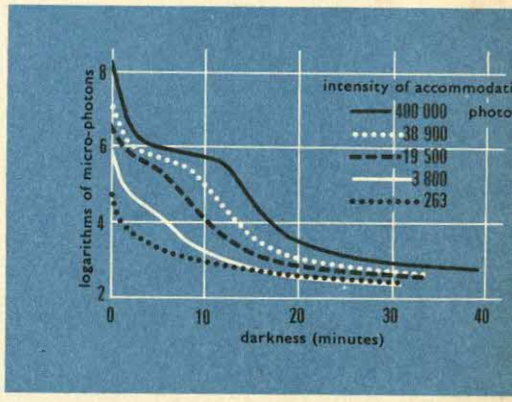


*Fig. 3. Curves of accommodation to darkness after two minutes of exposure to illumination of different intensities.*

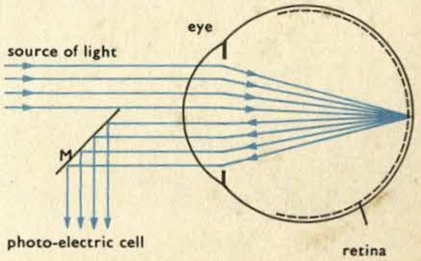


*Fig. 4. The principle of the ophthalmoscope. Light enters the eye through one half of the pupil and emerges through the other. The mirror M reflects the emerging rays on to a photo-electric cell. These rays pass twice through the retina (shown by a broken line).*

relatively insensitive but recover fast and within five minutes have reached their maximum sensitivity. Rods are much slower, only attaining equilibrium after half an hour, but at that stage they are much more sensitive than the cones. The two types of vision are independent and at threshold the eye responds to the most sensitive at the moment. At first, this is the cones, but later the rods exceed them in sensitivity, and appear as a curve rapidly falling below the horizontal cone curve. What is the rhodopsin regeneration doing while these rod-threshold curves are seen to be adapting a hundred-fold, or before that, when they are hidden above the more sensitive cones?

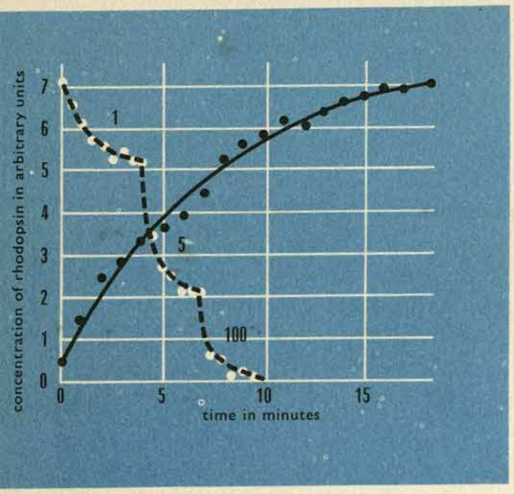


*Fig. 5. Breakdown of rhodopsin in the eye of the author (white circles) under the action of three equivalent sources of light of different intensity (1 unit = 20,000 photons). Black circles show the regeneration of the pigment in the dark (after Campbell and Rushton,* The Journal of Physiology, *1955).*

## *The measurement of visual pigments in the living eye*

When, driving a car at night, a cat by the road is caught in the glare of the headlights, its eyes shine back in a very striking manner. The light we see has been reflected from behind the retina and so must have passed twice through the retina and thus suffered absorption by the rhodopsin there, just as light through a church window is coloured by the absorption of some wave-lengths by the pigments in the stained glass. Clearly, the absorption will be less if the amount of rhodopsin present is less, and therefore changes in the rhodopsin concentration during bleaching, and regeneration can in principle be followed by measuring the change in the amount of light reflected.

Now, the *human* eye has not got behind it the splendid reflector of the cat's eye, but, like any good camera, it is lined with black. Thus only about 1/20,000th of the light entering returns for our analysis, and many precautions must be taken if trustworthy results are to be obtained. However, it is usually possible to measure at any moment the relative amount of rhodopsin in the human eye correct to about 0·05 of the total amount and the operation takes only about seven seconds to perform and may be repeated as often as desired. Fig. 4 shows the optical arrangement (ophthalmoscope) by means of which the in-going and out-going light can be separated, the latter analyzed in a photomultiplier cell. Fig. 5 shows one of the first rhodopsin measurements to be made upon a living human eye. They were made by Dr F. W. Campbell upon the left eye of the writer. Light of intensity 1 unit bleaches rhodopsin at first fast, later, more slowly and an equilibrium is reached at about

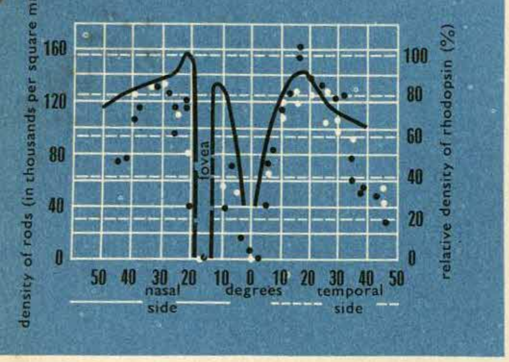
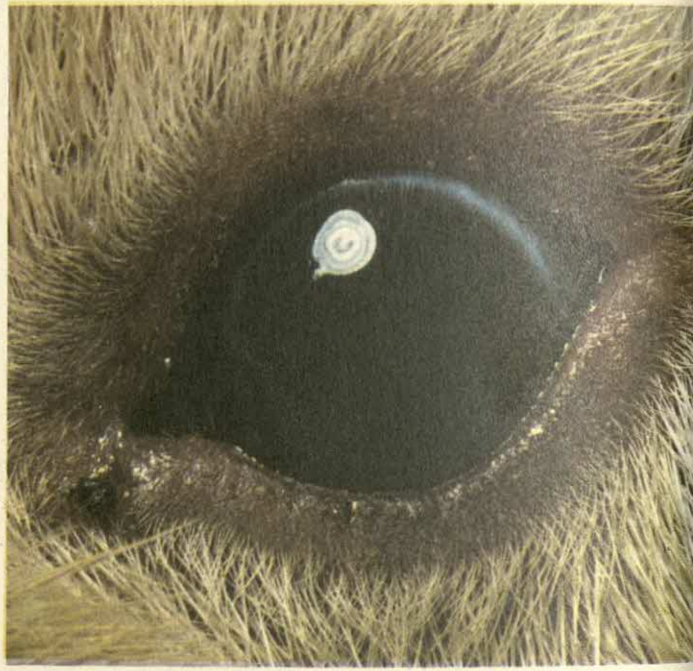


*Fig. 6. The white and black circles represent the quantity of rhodopsin in different parts of the retina, starting from the fovea. The curve shows the density of rods and cones in the different regions, according to Osterberg (after Campbell and Rushton,* The Journal of Physiology, *1955).*

*a*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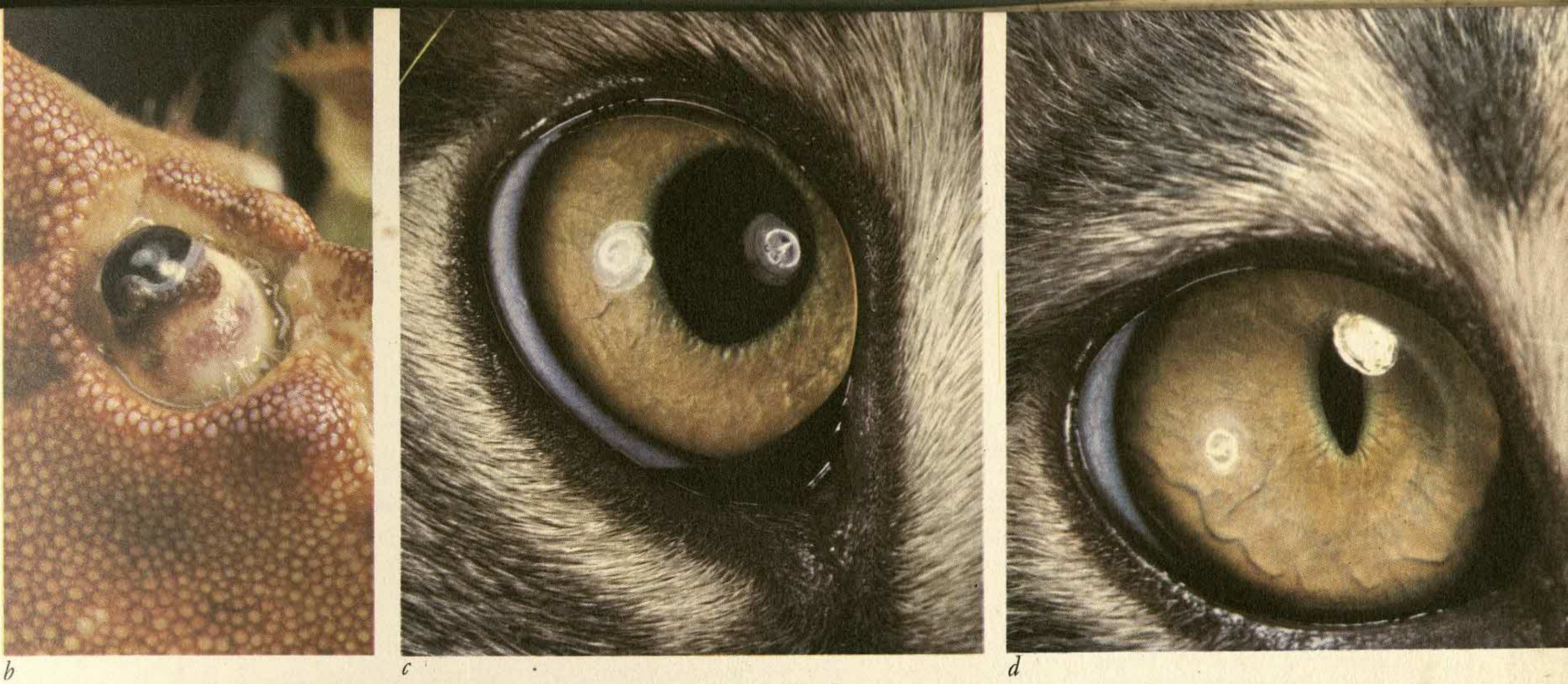
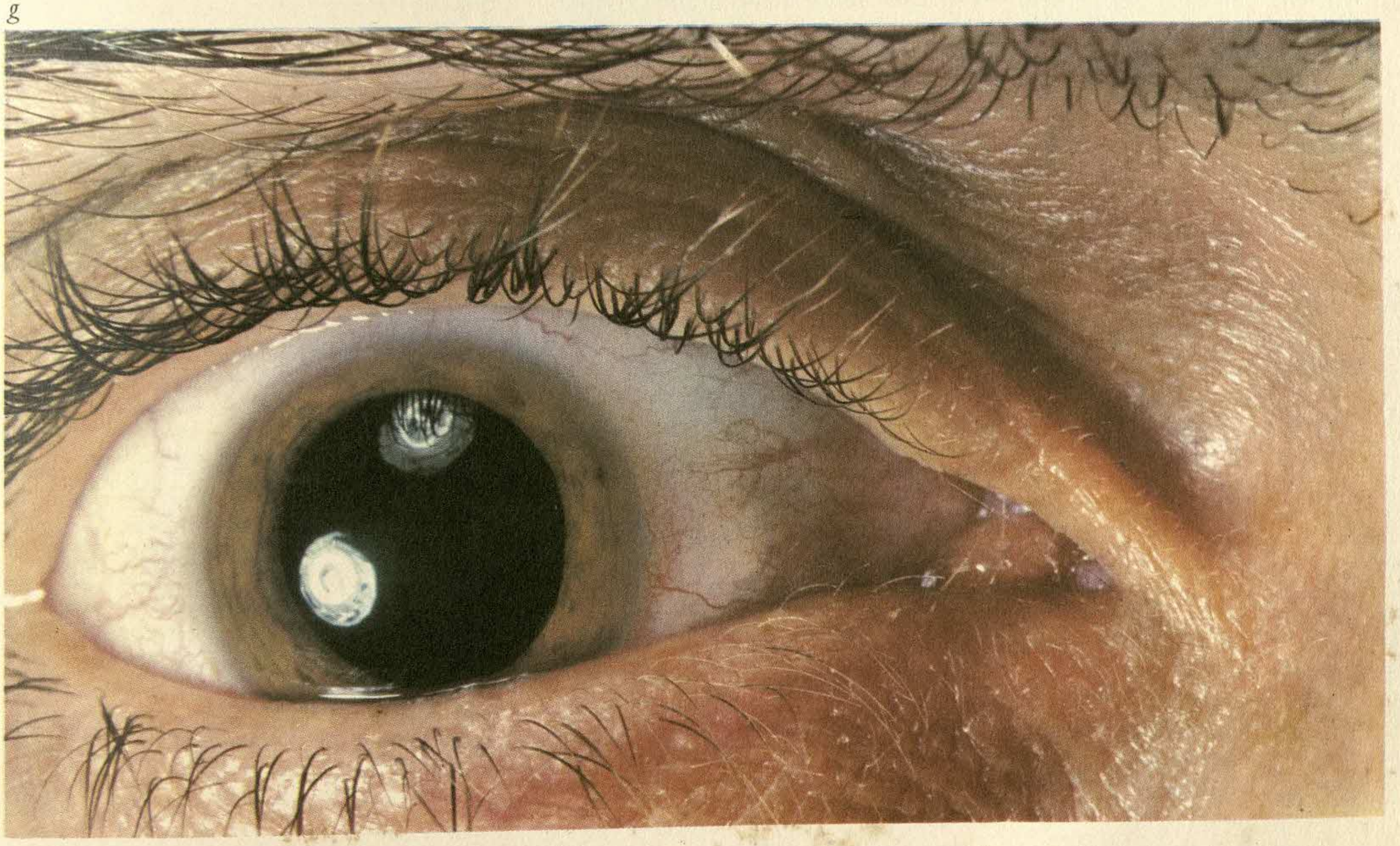


*The sense of sight is of such significance in the physiology of animals, especially the higher animals, that the eye plays an important part in the survival of species. Here are shown the eyes of different classes of animals: (a) fish; (b) crustacean; (c) cat with open pupil; (d) with pupil almost closed; (e) guinea-pig; (f) fowl; (g) man. (Photo Lod).*



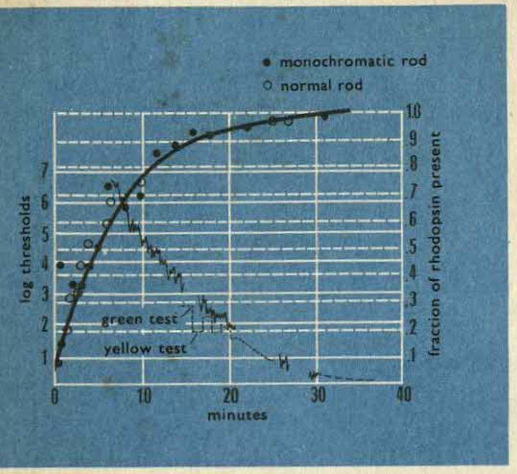


*Fig. 7. Regeneration of rhodopsin in the rods of a normal person (white circles) and of a person not possessing cones (black circles). The irregular line was traced by the latter during dark-adaptation. The dotted line is that of a normal person in these conditions.*

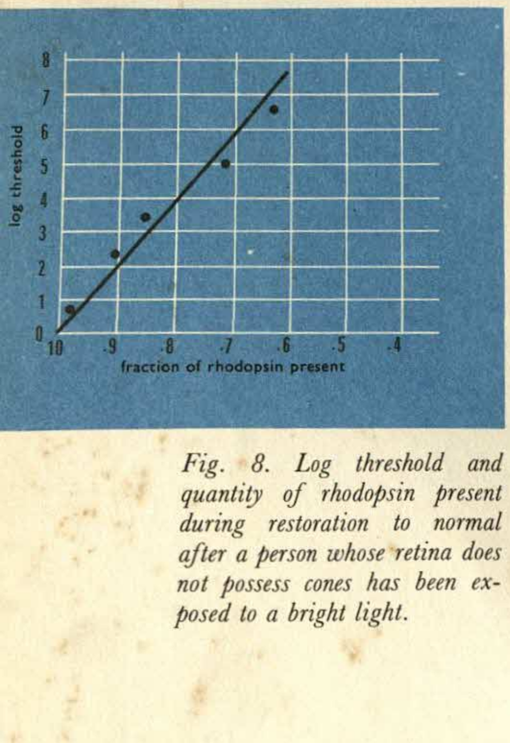


*Fig. 8. Log threshold and quantity of rhodopsin present during restoration to normal after a person whose retina does not possess cones has been exposed to a bright light.*

20 per cent bleached, where the rate of bleaching is exactly compensated by the rate of regeneration. A stronger light (5 units) bleaches faster and equilibrates at a higher level. Light of 100 units bleaches everything. For comparison with fig. 3, it may be stated that 1 unit was 20,000 photons. The black dots of fig. 5 show the regeneration of rhodopsin in the dark and it is seen that this does take certainly more than the eighteen minutes recorded to reach completion.

Fig. 6 indicates by two techniques (white or black dots) the total amount of rhodopsin in various regions of the retina. It is known that the mosaic of rods is not uniform but that in some regions they are packed tighter than in others. Naturally, it would be expected that where there are most rods there would be most rhodopsin, and in fact the dots follow the general course of the curve which represents Østerberg's microscopic study of rod-packing.

A comparison of fig. 3 and fig. 5 gives an indication of how far rhodopsin must have regenerated before the rods become more sensitive than the cones. The highest curve of fig. 3 represents recovery from bleaching which was about 90 per cent complete and the rod branch starts after thirteen minutes of dark-adaptation. But from fig. 5 it is seen that after thirteen minutes of dark-adaptation rhodopsin has regenerated to within about 10 per cent of completion. Thus the entire course of rod regeneration, though covering a range of 100-fold or more, is associated with the last 10 per cent of rhodopsin to regenerate.

Hecht's suggestion, then, that dark-adaptation waits upon the regeneration of rhodopsin appears to be true, but the high threshold after light is certainly not due to the inability of rhodopsin to catch quanta, but rather to the eye's relative inability to make use of these catches.

We can measure the whole time-course of rhodopsin regeneration, but we cannot compare the early part with the rod threshold (fig. 3) because this is hidden by the greater sensitivity of the cones. If only there were a region of retina where cones were absent, as rods are absent from the fovea, we might make some extended correlation between bleaching and log threshold. In fact, there is no such region of the retina, but there is a rare congenital condition where a person has practically no cones in his eyes, but rods are normal. Fig. 7 is from a girl with this condition.

The black circles show the regeneration curve of her rhodopsin, which follows the normal curve (white circles). The irregular line was traced by the subject during dark-adaptation and represents levels where alternately she could and could not see the test light. The curve is without an early cone branch, it starts more than a million times above threshhold and falls along a smooth curve to the normal dark-adapted value. The dotted curve represents the normal eye in the same condition. Up to about eighteen minutes of dark-adaptation normal vision is by cones, but when eventually the rod threshold appears, it coincides with the curve of the cone-less girl. We may therefore conclude that her curve is what the normal curve would look like if it were not screened by the cones, and plot the log threshold against the fraction of pigment bleached. This has been done in Fig. 8, whence we see that the two are proportional, as has been suggested by Wald.

## *Cones and colour vision*

The fact that we can see colours, and see them with our rod-free fovea, and cannot see them in twilight, when rod vision is being used, shows that colour vision is cone vision. And the well-known facts of trichromacy require that there should be three kinds of cone, each with a different visual pigment, or something more complicated upon these lines.

Now, no one has ever seen rhodopsin or any other visual pigment in the cones, nor has the technique of extraction which has proved so successful for rhodopsin ever yielded any other visual pigment from the eyes of man or any mammal. However, our reflection technique, which in fig. 6 measured rhodopsin in most regions of the retina, but not upon the fovea, can also analyze the visual pigments upon the fovea, and these are the pigments of cones and of colour vision.

In a series of experiments carried out on red-blind persons (protanopes) the author found evidence for the existence in the cones of two types of pigments, present in the normal eye, which preferentially catch the red quanta and green quanta, and therefore may be called *erythrolabe* and *chlorolabe* respectively. The probable existence of a third pigment, *cyanolabe,* is more difficult to detect.

The fascinating subject of colour vision is full of problems, and the sensitive pigments lie at the very first step of an exceedingly complicated process. But in the red-green range of the spectrum this step at least is becoming clear. For here the normal eye catches quanta with the two pigments erythrolabe and chlorolabe in proportions which depend upon the colour of the light.

# Colour vision

*Yves LE GRAND*

Long ago, two sorts of colours were distinguished, the 'false' rainbow colours of a prism or of the breast of a pigeon, which changed with the conditions under which they were observed, and the 'true' and solid colours of objects which were interpreted as being a mixture of light and darkness. This distinction is soundly based. The colours of the first type are due to the effects of dispersion[1] and interference[2] of the light itself, while those of the second type are caused by a partial absorption of the light at the surface of the objects which are illuminated. A red object does not add some mysterious red property to the uncoloured light which reaches it; on the contrary, it retains part of the light and the remainder, which reaches our eyes, is seen as red as a result of selective absorption.[3] It was also noticed quite early that certain colours appeared to be simply red, yellow and blue, while the others appeared to be made up from these three.

The technique of identifying colours is based on the study of mixtures, but we must first define this ambiguous word more carefully. The mixture is said to be subtractive on the palette, since each pigment takes away something from the white light. For example, a blue pigment absorbs the longer wavelengths of the spectrum, a yellow pigment absorbs the short ones; a mixture of these diffuses only those wave-lengths that are not absorbed by either, ie, the middle of the spectrum, which is green. Subtractive mixtures are used in colour photography, the film having three coloured layers superimposed on one another.[4] In this case the subtraction is no longer the result of a homogeneous mixture, but of the passage of light successively through coloured filters (fig. 1*a*).

Additive mixture is quite different and can be demonstrated by the use of three projectors, the light from which is coloured by filters. The lights are made to mix additively by superimposing them as they fall on a white screen (fig. 1*b*). In this case the addition of yellow and blue light gives a whitish result which is totally different from the green produced by the subtractive method. Yellow, a most unexpected result, is produced by adding red and green light. In fact, the laws of additive mixture are much simpler than those of the subtractive type. Thus they are to be preferred for colorimetry. In this technique a coloured light of unknown quality is matched visually with an additive mixture of the three fixed or primary colours in suitable proportions. This method, which is called trichromatic synthesis, is clearly only possible because of the trichromatism of our visual apparatus. In fact, it brings up certain difficulties which must be mentioned here to avoid confusion and misunderstanding.

The diffusing white screen E (fig. 2*b*) is divided into two by means of a perpendicular opaque partition in line with which the observer is placed. The left side is illuminated by the light to be determined, S. The right side is lit by the superimposed primary coloured lights, R for red, G for green and B for blue. Using control knobs, the observer changes the quantity of light from each primary until the lights on each side of the screen appear to match exactly. One then says that there is metamerism[5] between S on the one hand and R plus G plus B on the other. This metamerism in no way implies that there is a physical identity between the two lights but simply that there is a physiological identity in their action on the visual receptors. Moreover, it is a relative identity, valid only for the observer who has done the matching. For another observer, also normal,[6] the result will be slightly different. It will also change as the observer ages, because the lens tends gradually to become yellow.[7]

In talking about metamerism we should note how the eye, thanks to the physiological trichromatism, is less demanding than the ear. A trained musician will be able to recognize each of the notes which make up a musical chord. A colour, on the other hand, however complex, can always be matched with a mixture of the three primaries, with one reservation. A trichromatic synthesis in the physical sense may seem to be impossible, since the

(1) Dispersion: *variation of the refractive index with the wave-length.*

(2) Interference: *reciprocal interaction between light rays which have taken slightly different paths.*

(3) Selective absorption: *an effect which depends on the wave-length of the radiation being considered.*

(4) *The first industrial process of colour photography (Lumière autochromes) used a process of addition by juxtaposition, analogous to the pointillism of certain neo-impressionist artists.*

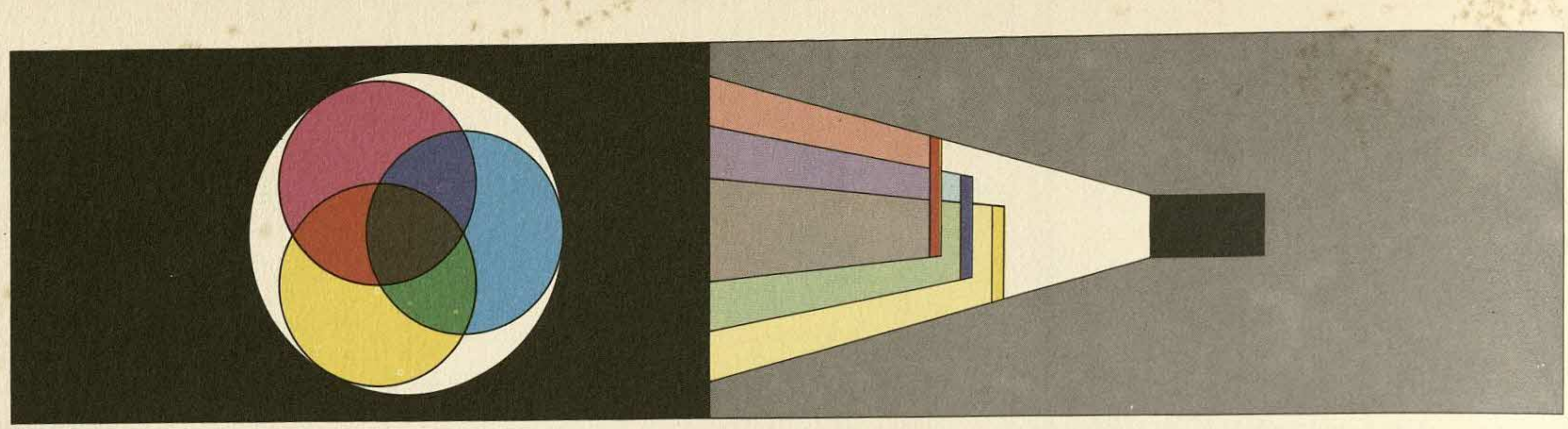
(5) Metamerism: *two lights are said to be metameric when they appear the same to normal vision, but are physically different.*

(6) *A 'normal' person as opposed to the dichromat and the abnormal trichromat.*

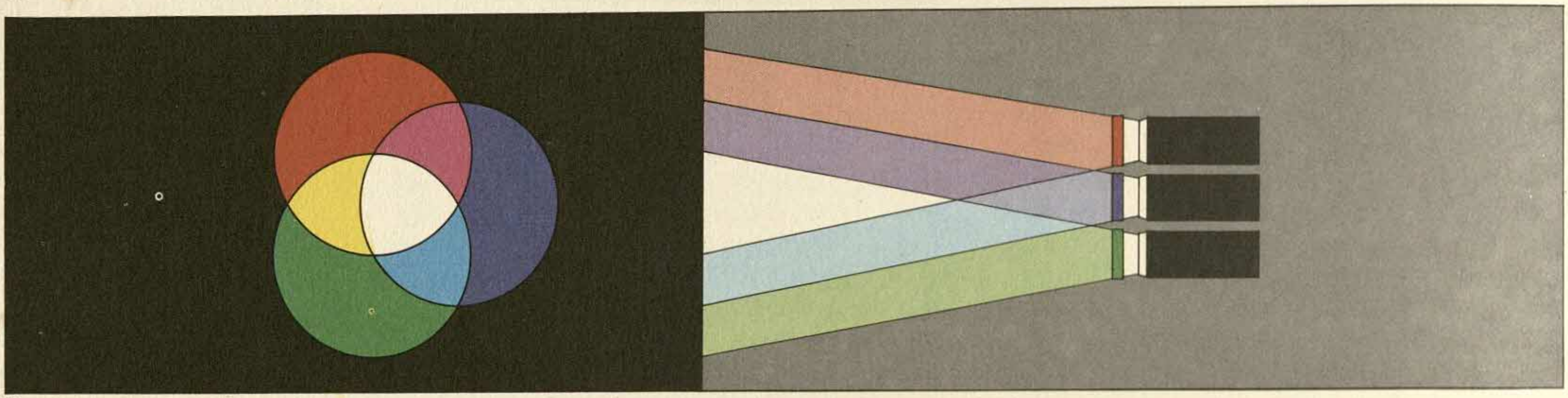
(7) *As a result, it is necessary to increase the primary blue. In order to avoid these individual differences in colorimetry, a fictitious ideal reference observer is used, a mean of normal persons about thirty years old.*

(8) Saturation *is maximum in the case of monochromatic radiation and is nil in the case of white light.*

(9) *Primaries are independent if it is impossible to make a metameric match between one of them and a mixture of two others.*

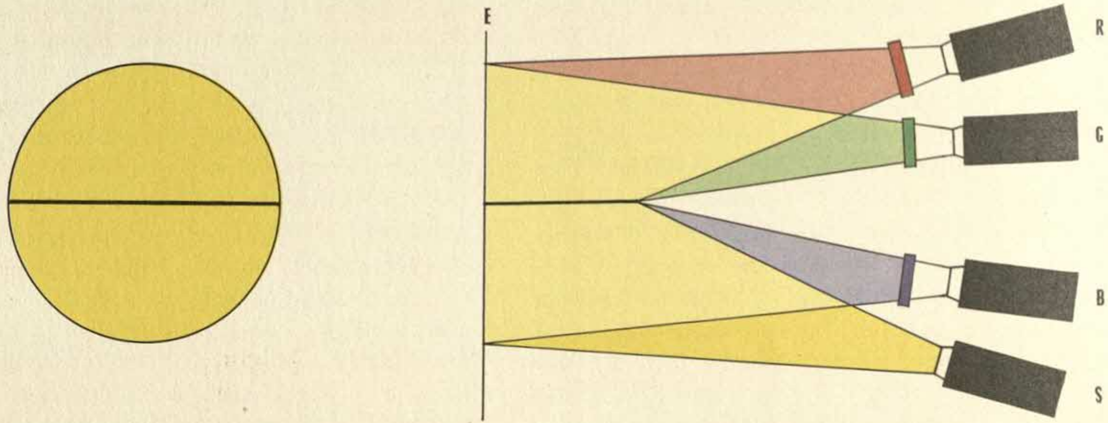


1a



1b

*Fig. 1. The principle of subtractive mixing (a) and additive mixing (b).*



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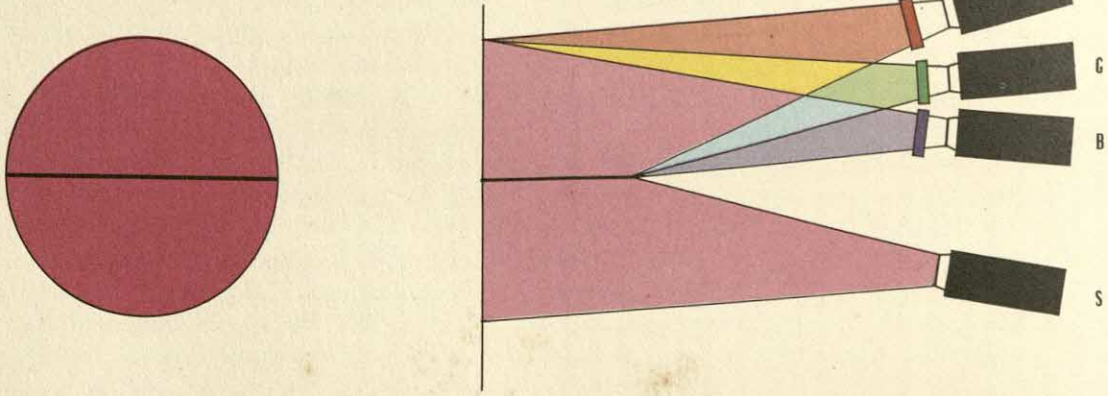


2a

*Fig. 2. The principle of trichromatic synthesis, without a negative component (b) and with a negative component, the primary blue (a).*

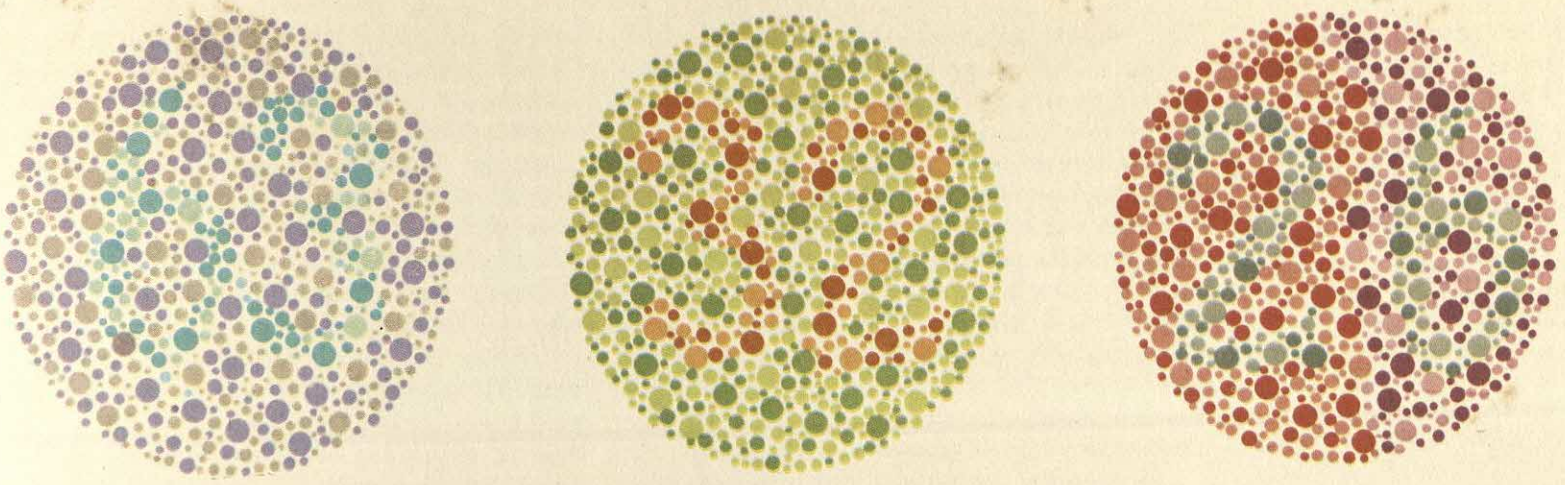
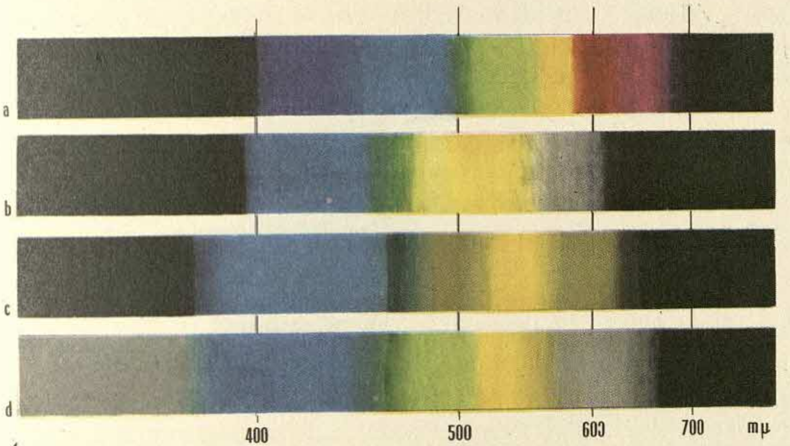


*Fig. 3. Detecting dichromats. A protanope cannot see the figure 2 on the red background and a deuteranope cannot see the figure 6 on the purple background because to them the background colours appear grey, being complementary (in normal persons) to the neutral band which separates yellow from blue in dichromats. (After Dvorine).*



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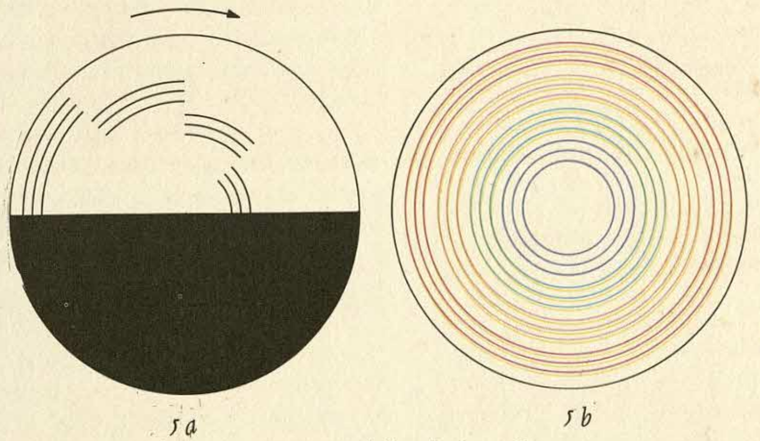
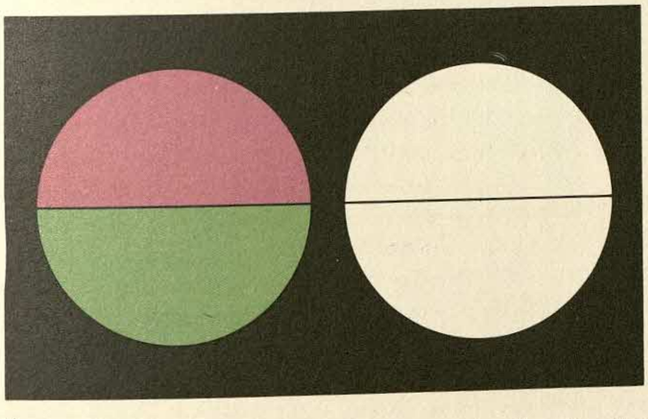
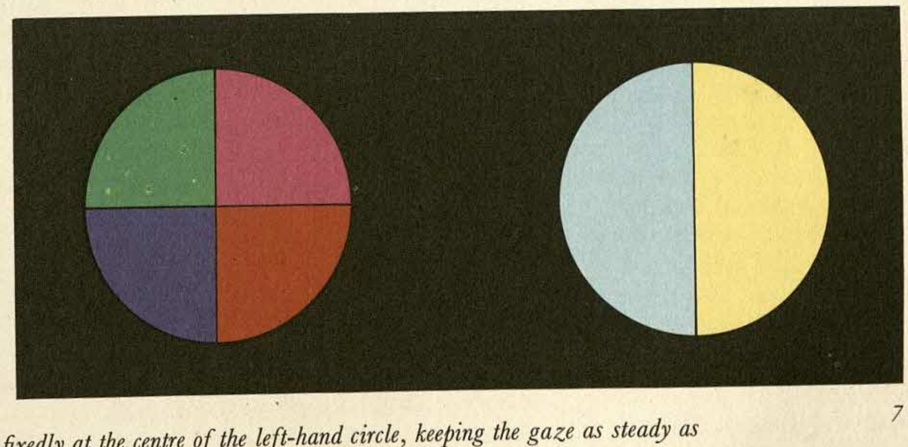


*Fig. 4. Diagrammatic representation of the spectrum as seen by* (a) *a normal person,* (b) *a protanope,* (c) *a deuteranope, and* (d) *a honey-bee. The 'colour' which the bee sees in the ultra-violet is represented by the shadowy grey.*

*Fig. 5. Subjective colours obtained by rotating the disc shown in* (a). *If it is turning at about ten revolutions per second under a bright light, one will see the colours as in* (b). *When it rotates in the opposite direction the colours appear in the reverse order. As Piéron has shown, this phenomenon arises from the difference in* latency *between the physiological primaries, which act differently with time.*





6

7

*Fig. 6. Successive contrast by adaptation. Look fixedly at the centre of the left-hand circle, keeping the gaze as steady as possible, then look at the centre of the right-hand circle. The contrasting colours will then appear.*

*Fig. 7. Demonstration of the dichromatism of small areas, after Willmer. From not less than twelve feet away, the left-hand circle will appear bicoloured and that on the right will appear uniformly coloured.*

light on the left always appears richer in colour and more saturated[8] than that on the right. In order to obtain metamerism in this case, it is necessary to take one of the primary colours over to the left (fig. 2*b*). There is still visual equivalence between S and the sum of R plus G plus B, but we assume conventionally that one of the primary colours appears with a negative sign (in Fig. 2*b* it is the blue component which is negative, since physically there is metamerism between S plus B on the one hand and G plus R on the other). This introduction of negative values into colorimetry is often difficult for beginners to understand.

One other important point should be noted. The primary colours may be arbitrarily chosen, provided only that they are independent.[9] It is, however, advisable to choose primaries which are well saturated and far apart from one another, since under these conditions case *(b)* will occur more often than case *(a)*, and negative values will thus be avoided. This is the reason for the normal choice of a red and a blue-violet very near the ends of the spectrum, and a green at the centre. Conversely, in subtractive mixing the best primaries are yellow, blue-green and reddish purple.[10]

## *Theories of colour vision*

Since, according to Young, trichromatism is a property of the retina, it is very tempting to explain colorimetry by the existence of three photosensitive pigments which would be situated in the retinal cones, the cells concerned with colour vision. Up to the present, it has not been possible to isolate these pigments, but Rushton has been able to demonstrate *in vivo* the existence of two of them. They are *erythrolabe*, which absorbs the long wave-lengths of the spectrum, and *chlorolabe*, which absorbs wave-lengths towards the centre of the spectrum.[11] It is probable that the chemical structure of these pigments resembles that of the rhodopsin of the rods.

The simplest hypothesis is that three sorts of cone exist in the retina, each containing one of these pigments. But the anatomy of the retina shows that all the cones appear to be identical, or rather, that they change in shape progressively with distance from the centre. In addition, the way in which we see small areas of colour is not in accordance with this theory. When the apparent diameter of such an object decreases, trichromatism is replaced by a dichromatism in which the primary colour blue plays only a very small part (fig. 7). Finally, all colour tends to disappear, but red is the most resistant. These facts could be explained if there were a disparity in density, the 'red' cones being very close together, the 'green' less numerous, and the 'blue' still rarer; if this were true, however, a small white point of light should appear most often to be red, less frequently yellow (simultaneous stimulation of red and green) and only very seldom white, whereas it is the opposite that is observed.

These paradoxes can be resolved in two ways. First, all the pigments may be mixed in every cone; in fact, metamerism implies only that the action on the three pigments of the lights which are being compared will be identical, and this identity will remain however the three are distributed. Second, the lack of colour in small objects suggests that the perception of colour in all its details necessitates the stimulation of a large number of cones, that it is an interaction in the retina and not an elementary effect. Perhaps we shall soon have more information about this.[12]

While colorimetry is governed by simple additive laws, our colour sensations on the other hand show destructions, ie, neutralizations of chromatism. A mixture of two coloured radiations is always less bright, less saturated, than those which make it up, and this impoverishment of colour becomes total in the case of the complementaries, which, when added, give white light. White light itself, daylight, for example, is achromatic as a result of the reciprocal neutralization of the monochromatic radiations which make it up.

Yellow, however, is one sensation that does not seem to fit in with the trichromatic pattern. Colorimetry may teach us that there is metamerism between a yellow light and an additive mixture of red and green, but our consciousness refuses to see yellow as a reddish green. It seems to us an irreducible sensation, like red and blue, and perhaps even more than green, in which we might see blue and yellow (but perhaps in this respect we are remembering the subtractive mixtures which we used to make as children with our boxes of water-colours!).

Therefore, psychologists in trying to interpret colour sensation have always preferred the conception of Hering (1876) to that of Young. Hering put forward the idea of 'antagonistic pairs', yellow-blue and red-green, produced by two mechanisms which are susceptible to opposite stimulations and cancel each other out for the complementary colours. The physiologists replied that this type of mechanism had never been found in

(10) *In practical colorimetry results are represented by means of a system of primaries adopted by the I.L.C. (International Lighting Commission). These are imaginary primaries which are defined only in mathematical terms, but they have certain advantages, such as avoiding negative values. It should be noted that in judging metamerism the eye is used only as an apparatus, ie, to establish equivalence. Thus colorimetry in no way involves the study of colour vision, but simply identifies colours by a method founded on the trichromatic theory.*

(11) *See the preceding chapter.*

(12) *Spectrophotometric techniques similar to those of Rushton, but applied to a very small number of cones or even a single one, may soon be possible, thanks to progress in instrumentation. On the other hand, we may equally be able to study the details of the interaction of colours in the retina.*

(13) *Electrophysiological researches will certainly clarify these matters. The classic studies of Adrian, Granit, Hartline, etc, have opened the way and such studies are now well advanced.*

(14) *At the beginning of the present century this method was tried out for coloured cinema films.*

(15) *The* cortex *is the outer layer of the brain. The visual centres (striate area) are found at the back of the base of the cranium.*

(16) *This problem is dealt with in more detail in the chapter, 'Anomalies of the Sense Organs', in Volume 6.*

(17) *Dalton thought that his eyes contained an abnormal coloured substance. But the dissection he had demanded showed nothing of the sort. The anatomy of the eye in dichromats also appears to be normal.*

(18) *See the preceding chapter.*

the visual apparatus. However, in 1956 Svaetichin placed very fine electrodes in the retina of certain fish and found electrical potentials of which the sign varied with the wave-length, furnishing in this way a physiological basis for Hering's theory. Thus the trichromatic theory of Young rests solely on the existence in the cones of three pigments sensitive to light and the whole of colorimetry stems directly from this. The conditions of colour vision, on the other hand, are derived from the potentials of Hering-Svaetichin which are produced either in groups of cones or else in the nervous relays which follow these (bipolar cells). It must be remembered that the retina is a peripheral expansion of the brain in vertebrates, a very complex system of hundreds of millions of cells which interact and inhibit at all levels. All we can say for certain at present is that colour vision results from its activities.[13]

It must also be remembered that colour vision is a dynamic process. Subjective colours appear in the course of movement (fig. 5) and, conversely, temporary adaptation creates coloured effects or modifies them (fig. 6). These contrasts of colours, studied a long time ago by Chevreul, have recently become topical in the researches of Land into the possibility of producing satisfactory colour images in television by means of two pictures only—one black and white and the other coloured, red, for example—the greens appearing subjective by contrast.[14] Clearly, the result is less satisfactory than one provided by trichromatic synthesis, but for selected scenes the appearance is pleasant, and the eye is so content to see the colour that what is missing can be supplied by memory.

Beyond the retina the optic nerve reaches the relay centre of the geniculate bodies, and thence the impulses pass on to the cortex,[15] in the occipital region. In an animal, and even in man, if the skull is opened, one can pick up electrical signals from the brain linked with vision. Thus in the macaque monkey, de Valois (1958) has demonstrated cortical responses which seem to vary with the wave-length and are linked with colour vision in the animal. Cerebral electrophysiology is rich in possibilities and will certainly in the near future help greatly in the understanding of colour vision.

## *The colour-blind*

Finally, we must mention briefly the important problem of those who do not see colours as the majority of us do.[16] These people are more numerous than is commonly thought, forming 8 per cent of males (they are twenty times less common among females, on account of the mechanism of hereditary transmission). Three-quarters are abnormal trichromats, the other quarter dichromats, formerly called daltonians, after the chemist John Dalton, who was the first to study scientifically his own case in 1798.[17] For dichromats the world of colour is two-dimensional instead of three-dimensional, as with most of us. Dichromats fall into two principal categories, the protanopes,[18] who are insensitive to red and thus see a spectrum which is shortened on the side of the long wave-lengths, and the deuteranopes, for whom the length of the spectrum is normal. According to studies on rare individuals who have one normal eye and one which is dichromatic, the spectrum of such people has only two tones; that which is red, orange, yellow or green to a normal person, is yellow to them, while the violet and blue seen by normal persons is blue to them. In the transitional blue-green region they see only grey (fig. 4).

The coloured world of the dichromat is thus very limited. At a given illumination the total of colours which a normal person can distinguish runs into thousands. A protanope can see only seventeen and a deuteranope twenty-seven. From this we can derive tests which show up these abnormalities (fig. 3), but they clearly prevent dichromats from undertaking any tasks for which good colour discrimination is necessary.

In the last century, great hopes were placed in the study of dichromatism, since it was thought that this would lead to the discovery of the mechanism of colour vision. Unfortunately these anomalies are too complex and too variable for us to deduce much from them. It does seem, however, that in protanopes one of the pigments is lacking from the cones, while in deuteranopes there is probably a paralysis of the Hering red-green pair.

Studies in comparative psychophysiology have shown that the sense of colour is well developed only in the highest animal species, social insects on the one hand (fig. 4), and birds and some mammals on the other.[19] Among the latter, the primates, who feed largely on fruits, doubtless owe the development of their colour sense to the vital necessity of being able to find fruit in trees. As man descended from them in the course of evolution, the beauty of our coloured world would seem to have had its origin in a humble need for food.

(19) *The colour vision of animals is studied either through training, or by the use of certain special techniques such as the optic motor reaction in the presence of a moving cylinder bearing coloured stripes.*

### HISTORICAL NOTES

*17th century*

RENÉ DESCARTES (1638) *made the first attempt to explain colours by a physical property of light (rotation of luminous corpuscles).*

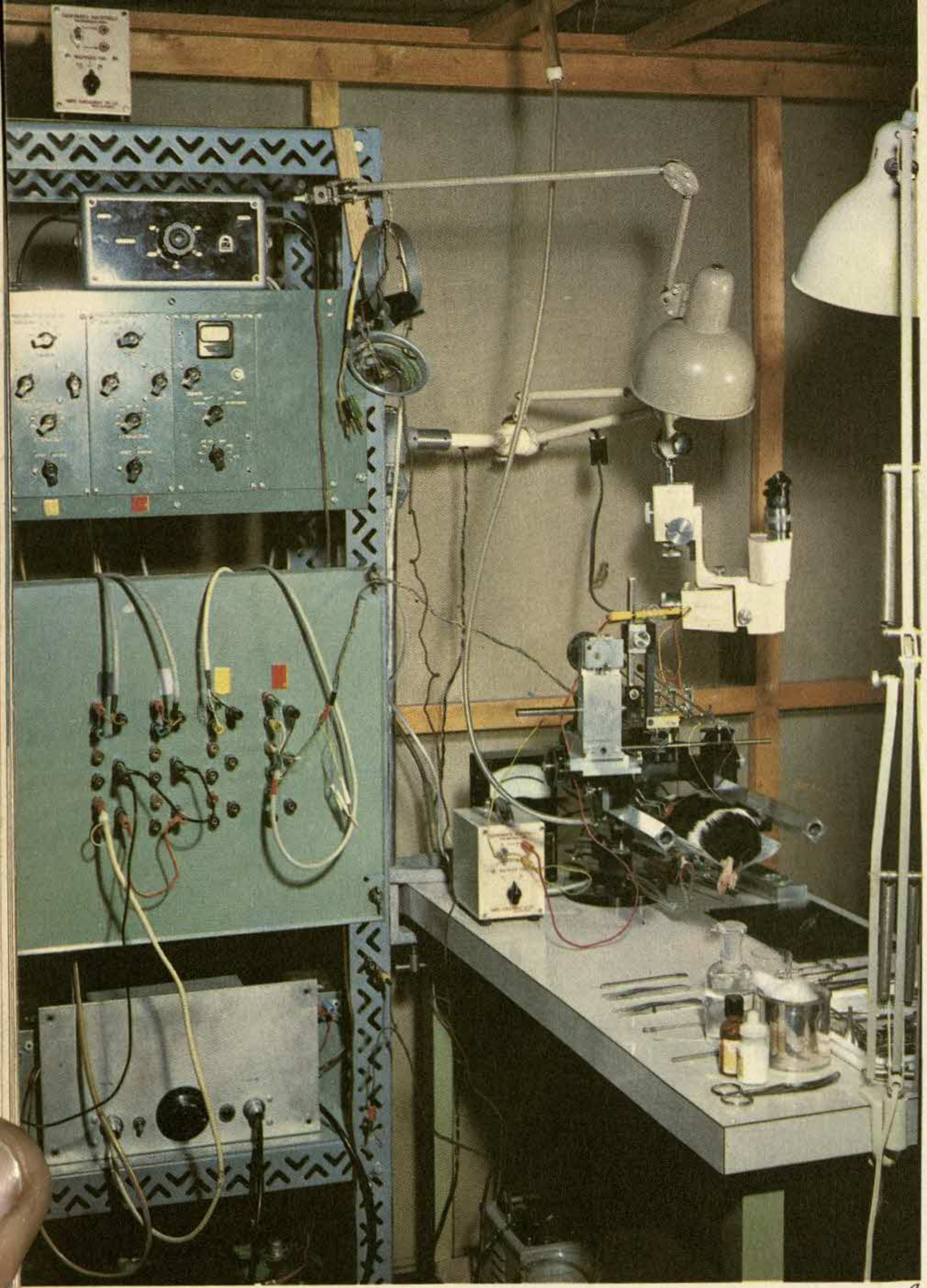
ISAAC NEWTON (1666) *undertook his celebrated experiments on the breaking-up of light by means of a prism. White light is made up of homogeneous radiations, called monochromatic, which are characterized by a greater or a lesser deviation as they pass through the prism. Newton thought of light as being made up of corpuscles of variable mass.*

*18th century*

LEONHARD EULER *established the first link between colour and wave-length for monochromatic light. Later, the quantum theory of light was to show that the mass of the photon is proportional to the frequency, and thus inversely proportional to the wave-length. Both Newton and Euler were right.*

*19th century*

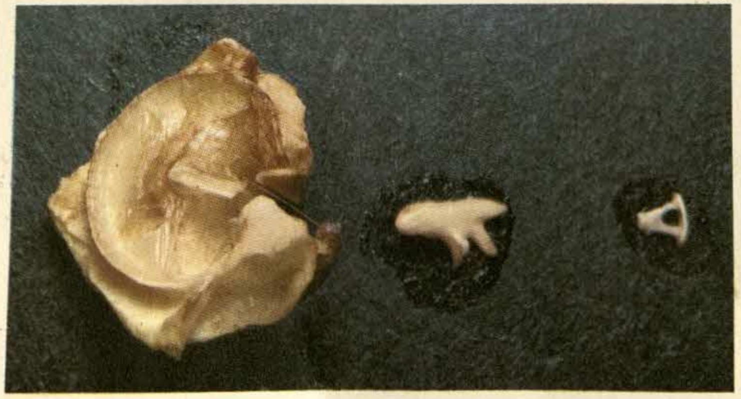
(THOMAS YOUNG (1773–1829), *doctor, physicist, and founder of optical physiology, the study of interference and hieroglyphics, had the fruitful idea of looking for the cause of trichromatism (the triad of primary colours) in the physiology of the eye rather than in the physical nature of light. According to his ideas, the three primary colours correspond to three receptive mechanisms in the retina, sensitive respectively to long, medium and short waves of the visible spectrum. The whole science of colorimetry which has arisen since the middle of the nineteenth century is based on this theory.*

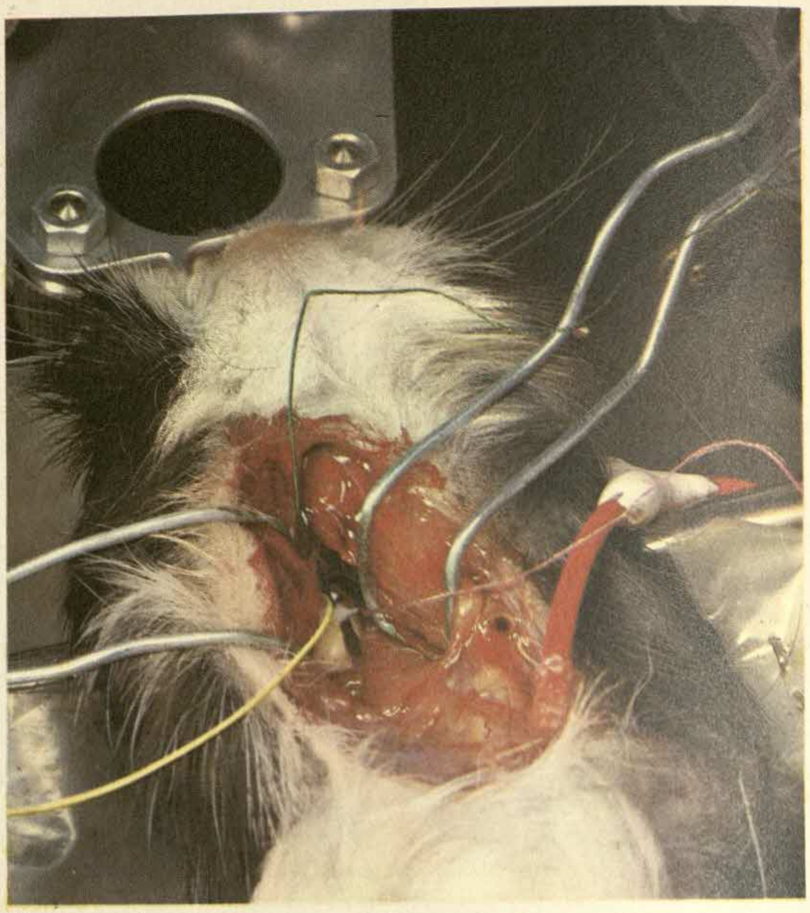


a

*In order to measure the acoustic stimulation in different parts of the ear, the scientist places electrodes in the tympanic cavity of a guinea-pig. (Photos Lod, taken in the Laboratory of Experimental Otoneurology of the Faculty of Medicine, Paris).*

b

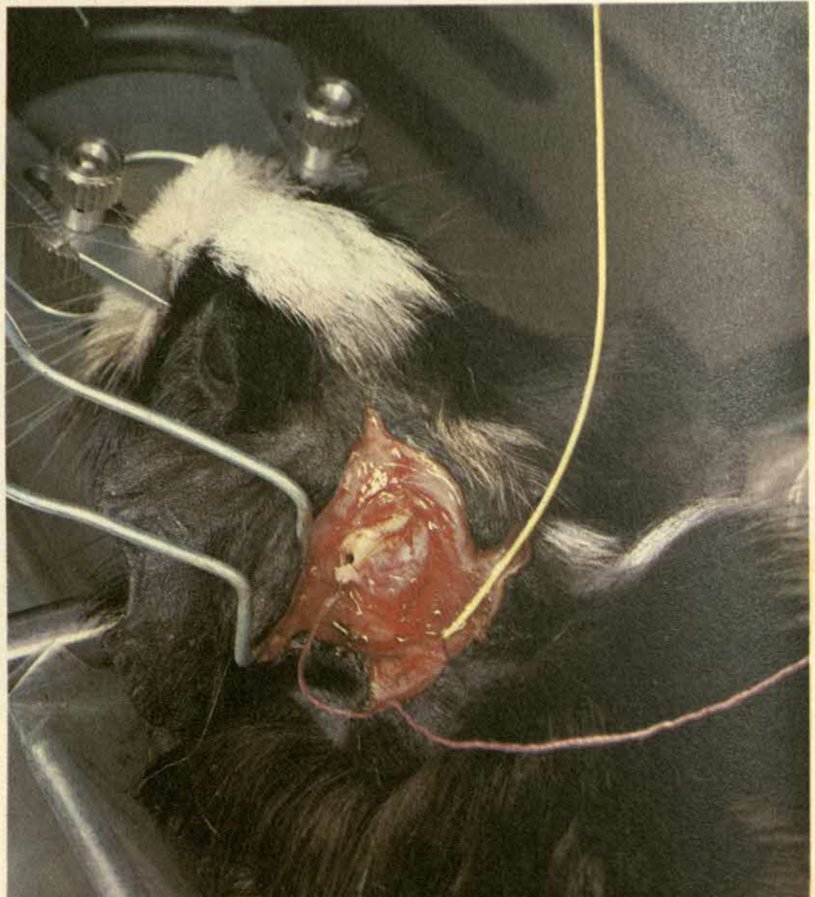




c

*In* (a) *we see a general view of the apparatus with a platform for the animal, the electrode carriers and the pre-amplifiers situated in a Faraday cage. In* (b) *are shown the chain of ossicles from a guinea-pig, showing particularly the difference in surface area between the ear drum and the foot of the stapes (stirrup). From left to right: the insertion of the handle of the malleus (hammer) into the ear drum (the ossicle has been sectioned), the incus (anvil) and the stapes (stirrup). In* (c) *and* (d) *the anaesthetized animal is operated on in order to have very fine electrodes placed in the cochlea.*

d



# Mechanisms of hearing

*Michel BURGEAT*

*The capacities of the ear, both in the analysis of frequencies and in the perception of the slightest sounds, are very considerable. We are all too often upset by the increasingly obtrusive sounds of our mechanical civilization; it is indeed remarkable what little energy is needed to produce a sensation of hearing. This wonderful sensitivity is due to the astonishing fineness of the auditory mechanisms.*

In order that a sound may be transmitted, it is necessary that the medium to which the source of noise is applied should be elastic and should react to deformation. Air, water, and steel are such media. The molecules that are in contact with the source are subjected to a force which causes them to be displaced—not far, of course, but enough to make them knock against their neighbours. The pressure which unites the molecules to each other, that is, the force of cohesion, ensures that these first molecules come back afterwards to their original places, opposing in this way any permanent deformation of the medium; an opposition which is the very quality of an elastic medium that will not lose its shape. It is the same for each succeeding group of molecules which, after displacing the next group, returns to its place. Thus a succession of pressure waves is produced, shifting by degrees, causing a sound wave with a speed in air of 1,115 feet a second.[1]

However, for the sound vibration to be perceived there must be somewhere in its pathway an organ capable of receiving it and transforming it into a sensation. This organ is, of course, the ear, which alone can bring about the transformation of this physical phenomenon into a physiological one. There are, for all that, certain limits outside which a wave shock will not be perceived by the ear. If the frequency is too low, we are dealing with infrasonics; if it is too high, with ultrasonics.[2] The displacement of the sound wave takes place concentrically from its source, in the same way as waves spread out over the surface of a pond after a stone has been thrown in. This displacement would continue indefinitely but that the force necessary for the shifting of the molecules becomes progressively exhausted through the very resistance opposed by the medium.

Thus a second limit to the production of a sensation of sound is introduced. In the same

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(1) *The* speed of sound *is here defined as being at a temperature of 0°C and atmospheric pressure at sea-level. In steel, the speed of sound is 1,640 feet per second and in reinforced concrete it is 3,300 to 6,600 feet per second.*

(2) *The* frequency *is the number of times a periodic phenomenon repeats itself in a given time. It is measured in cycles per second, or Hertz, and can be represented as a sinusoidal curve.*

(3) *This limit varies with age. Hearing diminishes more or less with time. It is especially the perception of sounds of high frequency which diminishes in the course of ageing of the ear; this is called presbyacusis.*

(4) *The* decibel *(dB) is one-tenth of the bel, the unit of measurement of sound which allows us to express a sound in terms of a pressure ratio, in accordance with the classic laws of Weber and Fechner. This is a logarithmic scale which extends from 0 (the threshold of hearing) to 120 (the highest intensity that can be heard without causing pain).* $N$ *(in decibels)* $= 10 \log_{10} P_1/P_2$.

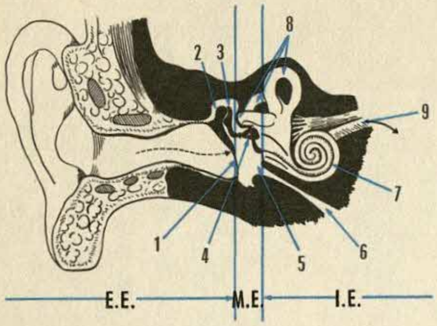


*Fig. 1. A sectional view of the ear, showing the external ear (E.E.) the middle ear (M.E.) and the inner ear (I.E.). (1) ear-drum; (2) malleus; (3) incus; (4) stapes; (5) middle-ear cavity; (6) Eustachian tube; (7) sensory cells of the cochlea; (8) semi-circular canals; (9) auditory nerve.*

way that the ear cannot detect sounds of too low a frequency (below 20 cycles a second) or too high (more than 20,000 cycles a second),[3] so it cannot detect sounds even of a normally audible frequency, if the intensity is too low. There is thus a threshold of intensity below which the vibratory wave cannot produce a sensation of sound. At a frequency of 1,000 Hz, the frequency best heard by the human ear, the threshold is reached at a power of $10^{-16}$ watts per square cm, which corresponds to a pressure of 0·002 dynes per square cm at sea-level and at a temperature of 23°C. On the scale normally used in psycho-acoustics this threshold value is expressed as 0 decibels (0 dB).[4]

Thus if the wave passing through the air has a frequency between 20 and 20,000 Hz and has a sufficient amplitude, an ear placed in the sound field will transform this physical energy into a sensation of sound. The sound wave which enters the ear will follow a well-defined and very complex path.

## The external ear

Most animals that need to catch slight sounds and to determine with precision their place of origin (for on this their own safety may well depend) have a conch-shaped, elongated, mobile organ, called the external ear. Man also has this auricle, which forms the only exterior indication of the auditory organs, and the importance of which is much less than that of the other parts of the ear. At the most, it may concentrate the sounds, direct them towards the external auditory meatus, and play some part in determining the direction from which they come.

In the centre of the external ear there is the round opening by which the sound enters the external auditory meatus. In the adult, this meatus, roughly cylindrical, is about 7–8 mm in diameter and about 25 mm long. The sound wave travelling along this meatus cannot do so without the walls reacting, as happens in any closed sound-producing pipe. In fact, it creates what is called a 'complex acoustic field' and the meatus thus acts as a resonator which will favour a certain part of the sound spectrum.[5] Thus this external meatus cannot be looked on as an entirely passive structure in hearing, especially since it has also the role of protecting the deeper and more sensitive parts from any traumatism from outside, both by the twisting character of its path and by the secretion of cerumen, or wax.

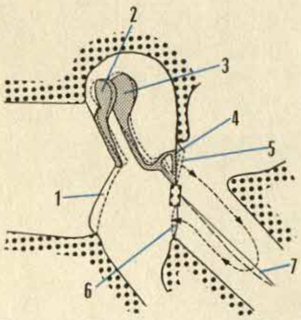


*Fig. 2. The movement of the ossicles: (1) ear-drum; (2) malleus; (3) incus; (4) stapes; (5) fenestra ovalis; (6) fenestra rotunda; (7) basilar membrane. (After Stevens and Davis).*

## The ear-drum

When it arrives at the bottom of the external auditory meatus, the sound wave reaches the first obstacle placed in its way by the ear—the ear-drum. This is a fibrous membrane, rounded in shape, with a surface area of about 85 square mm. It seals hermetically the bottom of the external auditory meatus. It is made up of two types of fibre which have conflicting actions but whose tensions balance each other. The drum thus has two essential acoustic properties: it is rigid enough to vibrate, but also slack enough to deform without modification of its mechanical characteristics. It is, in short, the first active element in the process of hearing, the first obstacle in the path of the molecular shocks in the air. Its role is to receive the sound which has so far been propagated in the air, and to change its medium. For the first time, the sound leaves its natural medium, the air, and penetrates into the depths of the ear to set in motion the subtle mechanisms of hearing.[6]

## The middle ear

Beyond the drum begins what is called for convenience the middle ear, formed principally by the tympanic cavity. This small cavity is roughly prism-shaped with a volume of 1–2 cubic cm. It is hollowed out of the mass of a thick, solid bone: the petrosal bone. This bone, shaped like a pyramid with its base outwards, meets at its apex with that of the opposite side. It is one of the important structures of the skull, and embedded in it are the middle ear and the inner ear. The outer wall of the middle ear cavity is largely formed by the drum, while its inner wall abuts on to the inner ear. This drum has walls lined with mucous membrane and it communicates with the mastoid cells and with the outside air through the Eustachian tube. Since the drum forming the outside wall is in direct contact with the outside air, the outside wall is always exposed to the pressure of the outer atmosphere. So that the air in the interior may be at the same pressure, there must be a communication between the interior and the outside. This is the role of the Eustachian tube, which runs from the middle ear cavity down to the external wall of the naso-pharynx. The Eustachian tube is normally closed by a sphincter muscle, but each time swallowing occurs, the tube opens and allows the pressure inside and outside to equalize. If for any reason this fails to happen, pain and difficulty

(5) *According to measurements made by Bekesy, the external auditory meatus provides a zone of resonance between 2,000 and 3,000 Hertz.*

(6) *The amplitude of the vibration of the ear-drum over the most sensitive region (2,000 to 3,000 Hertz) is less than the diameter of a hydrogen molecule. The effective mobile surface, according to Bekesy, is 55 square mm, or about two-thirds of the total surface.*

in hearing may occur, as may be noted when climbing a mountain or flying in an aeroplane.

The sound, which has until now been travelling along the external auditory meatus, must, in order to reach the inner ear—an essential stage in hearing—pass from the ear-drum to a small hole on the inner side of the middle ear. This opening, which has a surface area of about 3 square mm and is called the oval fenestra or window, puts the sound vibration in contact with a new medium, this time a fluid, at the surface of which the arriving energy would risk being reflected and lost, if it were not for a chain of ossicles, since the impedances of the two media are so different.

There are three ossicles: the malleus, the incus, and the stapes (hammer, anvil, and stirrup), and these ensure that the sound waves pass without loss from the air of the external ear to the fluid in the cochlea of the inner ear, by acting as transformers of impedance.[7]

## The ear ossicles

The ossicles are held in place by ligaments fixed to the walls of the drum and these allow motion about certain axes. The articular surfaces ensure a tight but mobile contact between them. They can thus move in relation to each other while still remaining firmly in contact (fig. 2).

The malleus, which, like the other ossicles, takes its name from its shape, is the outermost of the chain. Its handle is inserted into the thickness of the ear-drum itself, so that the vibrations caused by the sound waves striking its outer face are easily transmitted onwards.

The incus, which follows and is the biggest of the three ossicles, acts as an intermediary and transmits the vibrations from the malleus to the third ossicle, the stapes, the flat foot of which fits into the fenestra ovalis on the internal wall of the drum.[8] It is the stapes which passes the sound wave to the cochlea where it is turned into the perception of sound.

The foot of the stirrup (stapes) moves to a variable extent, depending on the intensity of the sound. In the case of low intensities it is pushed very gently into the fenestra ovalis, like a little door with the hinge behind, but if the sound is very loud it is slightly rotated in order to protect the cochlea.

In the case of low intensities, the joints between the ossicles do not seem to play a very active role in the transmission of sounds, unless it is in the surface of contact they offer to each of the ossicles, which vibrate as a whole. The transmission of sounds does not, indeed, come about by means of a lever mechanism, as Helmholtz thought. On the other hand, in the case of loud sounds, the ossicles, moved by their muscles, will pivot slightly at the articulations in order to protect the ear.

## The muscles of the ear

There are in the middle-ear cavity two little muscles which are called the muscle of the malleus (tensor tympani) and the muscle of the stapes (stapedius), because they are inserted on those ossicles. The contraction of these muscles controls the tension of the ear-drum and the extent to which the stapes enters into the fenestra ovalis. Their contraction is a reflex phenomenon affecting both ears. When the muscle of the malleus contracts, it stretches the ear-drum and pushes the foot of the stapes into the fenestra ovalis. The contraction of the muscle of the stapes, on the other hand, relaxes the drum and pulls the stapes out of the fenestra ovalis.

The part played by these muscles in the transmission of sound is a complex one. At low intensities the stapedial muscle acts as a regulator, tending to bring the vibrations to a frequency of 1,500 Hz. At high intensities of sound both muscles enter into action in order to protect the inner ear from the effects of loud sounds. Besides altering the response and protecting the ear, the muscles help transmission by maintaining the correct tension between the ossicles so that they function most efficiently (Bekesy).

## The internal ear: the cochlea

Situated in the depths of the petrosal bone, the inner ear, that is the cochlea, is the site of a very remarkable phenomenon which even now is not well understood. Up to this point, and all along their path through air,[9] the sound waves have been only a physical phenomenon which can be explained without much difficulty in terms of the ordinary laws of physics. Now, suddenly, this character disappears to make way for a new kind of energy transformation. Here the sound waves are turned into nerve impulses at the source of the sensation itself.

Most animals have some region in the body in which mechanical vibrations have the power of exciting nervous activity. In some this organ is not well differentiated, but as one ascends through the animal kingdom it changes and its possibilities increase considerably.

The human cochlea is about 35 mm long, straight at first and then rolled up spirally for two and a half turns. Its general shape is that

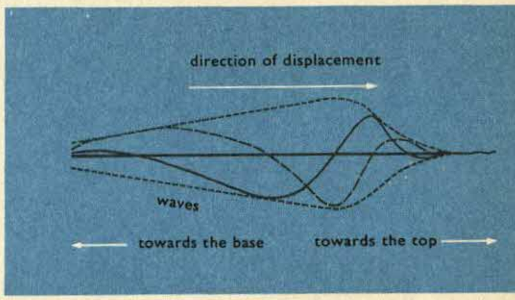


*Fig. 3. Waves passing along the basilar membrane of the cochlea. (After Bekesy).*

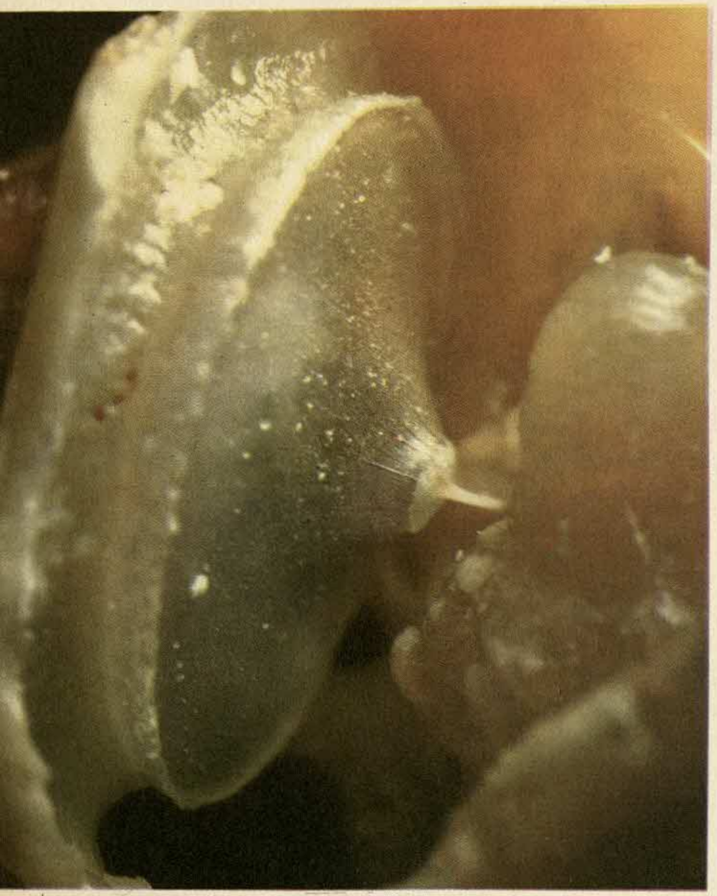
(7) *The ossicles also have two other roles: (1) to change the phase of the vibrations through 180° (the fenestra rotunda and the fenestra ovalis are thus opposed in phase) and (2) to amplify the acoustic pressure slightly (about twice).*

(8) *The ossicles weigh: malleus 2 mg; incus 27 mg; stapes 2·5 mg.*

(9) *As against the aerial route, the normal one for the passage of the sound waves, there is also a route directly through the bones of the skull, known as 'bone conduction'. This route leads to a loss of about 30 decibels compared with that through the air.*

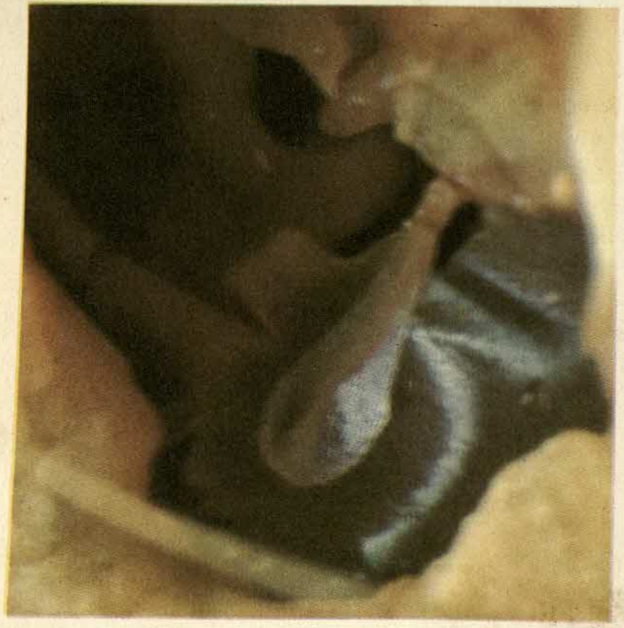
# *The middle and inner ear*

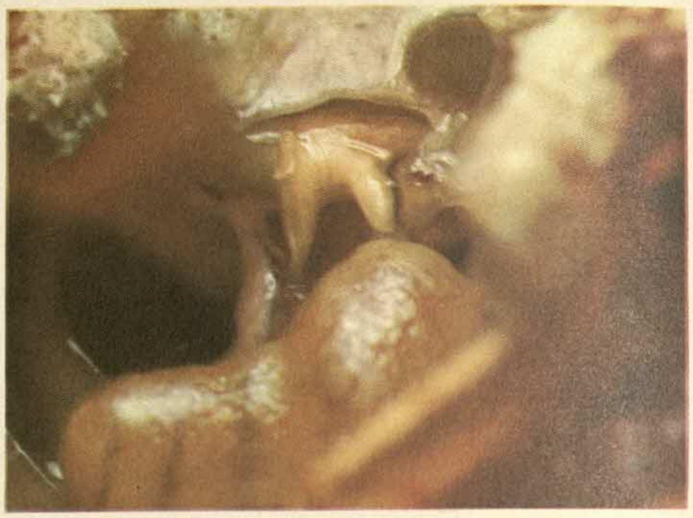
*These pictures show the main parts of the middle and inner ear of a guinea-pig. (Photos Lod).*



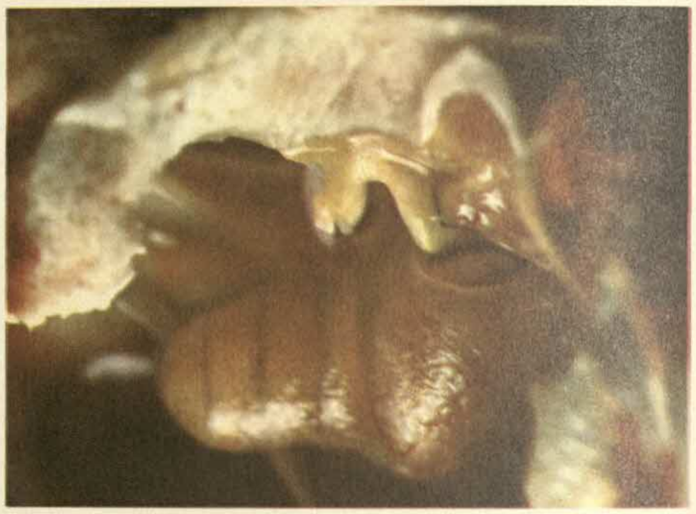
*The bony frame, showing the internal surface of the tympanum or ear-drum, with the insertion of the malleus.*

*The insertion of the handle of the malleus in the tympanic membrane, seen by transparency. The tympanum has been incised to show the incus, with the cochlea at the back.*

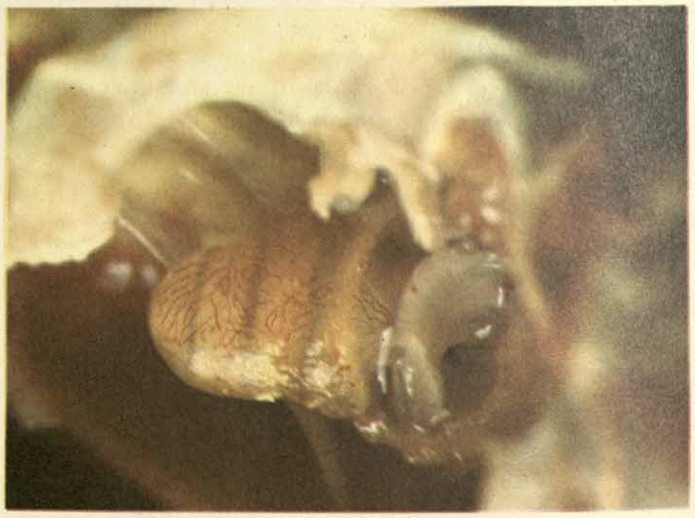




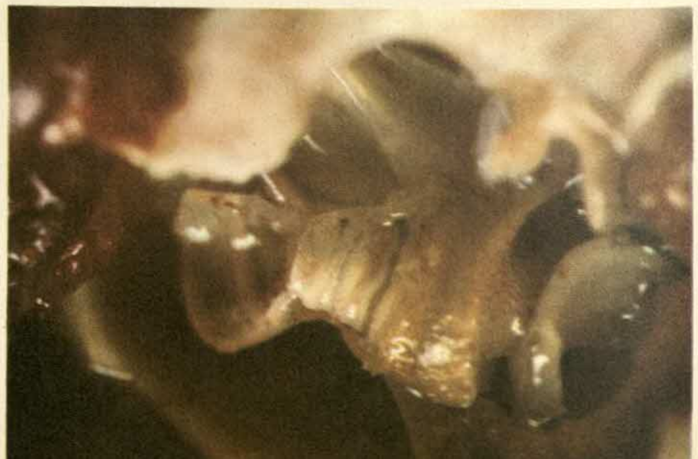
*The incus and its articulation with the stapes. Below, the cochlea.*



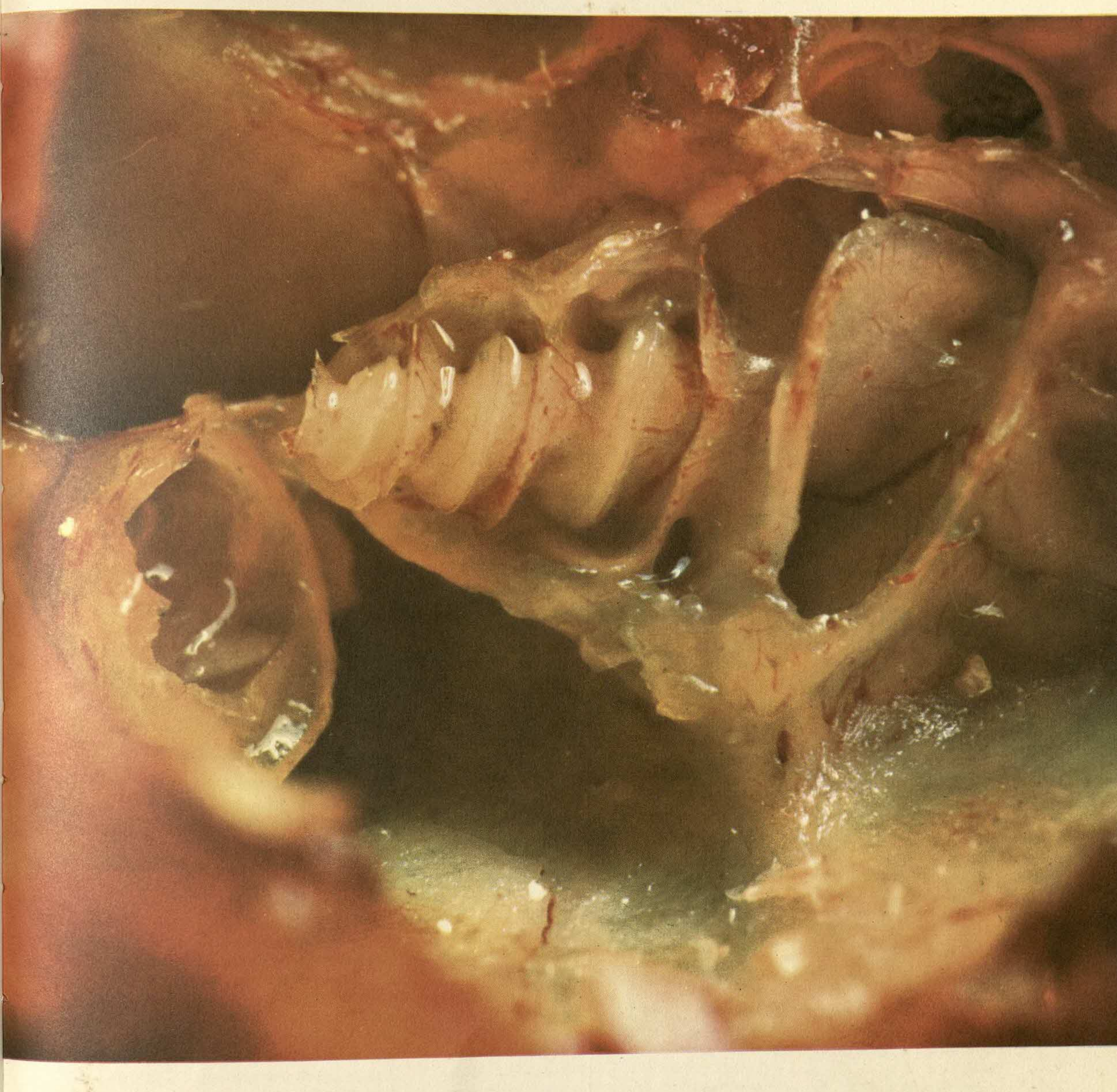
*The cochlea: the fenestra rotunda, the vascular striae and, above, the incus and its articulation with the stapes.*



*The cochlea: opening of the cochlea from the fenestra rotunda, the remaining edges of which can be seen above and to the right. Internal view of the spiral lamina and the scalae.*



*The cochlea: the top has been partially detached and lies to one side in order to show the spiral lamina and the scalae. The stria vascularis of the second turn is particularly clear.*



*The cochlea completely opened. One can clearly see the delimitation of the turns of the spiral and the spiral lamina separating the two scalae at each turn. In the centre is the columella, forming the axis of the spiral. (Photos Lod, taken in the Laboratory of Experimental Otoneurology of the Faculty of Medicine, Paris).*

of a cone; its base corresponds to the internal auditory meatus which is about 8 mm long and communicates with the cranial cavity. It forms a prolongation from the cochlea of a straight hollow tube, known as the 'columella'.

The columella, which forms the axis around which the cochlea is wound, is pierced by small orifices through which pass the bundles of nerve fibres coming from the sensory cells and which go to make up the cochlear nerve.

In the interior of the snail-like tube, which is more or less cylindrical and which narrows from base to apex, there is a second membranous tube that follows exactly the curvature of the bony shell. This membranous spiral is divided into three channels by two partitions: Reissner's membrane, and a bony lamina, the spiral lamina, which is itself extended by another membrane, the basilar membrane (fig. 5).

The two external channels are called the scala vestibuli and the scala tympani, and the central one between them is the cochlear duct. The scala vestibuli and the scala tympani are filled with a fluid, the perilymph. The fenestra ovalis opens into the scala vestibuli and the fenestra rotunda opens into the scala tympani. The two scalae separated by the cochlear duct extend along the whole of the spiral of the cochlea, and at the top the two scalae communicate with each other through a small orifice, the helicotrema, formed by a deficiency in the spiral lamina and the basilar membrane at their ends.[10] The perilymph communicates with the perilymphatic space of the vestibule and with the semi-circular canals, the organs of balance. It is also in communication with the sub-arachnoid space through a fine canal, the aqueduct of the cochlea.

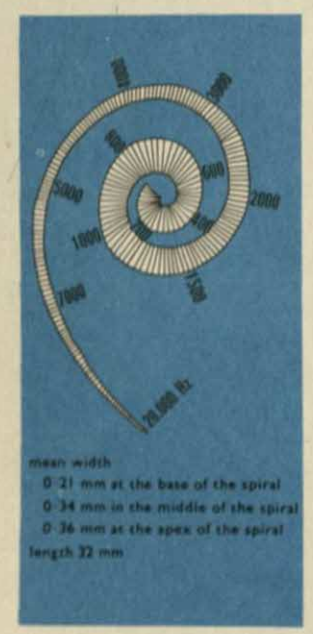
This arrangement is complicated only in appearance and it is necessary for the functioning of the inner ear. If we represent the cochlea diagrammatically in unrolled form as a horizontal U-tube, we see that one end of the tube ends at the fenestra ovalis (the scala vestibuli) and the other ends at the fenestra rotunda (the scala tympani). When the foot of the stapes is pushed into the fenestra ovalis, a pressure originating externally is transmitted to the perilymph. The displacement of the fluid which creates this compression is only possible because there is the deformable membrane, the fenestra rotunda, at the other end of the tube, which can move at the same time as the membrane covering the fenestra ovalis. In fact, the movement of the stapes in the fenestra ovalis leads to a displacement of the membrane covering the fenestra rotunda towards the exterior. This free interplay between the two fenestrae is essential for normal hearing, since the fluids involved are incompressible.

## *The organ of Corti*

Having reached the end of its journey, the sound wave has no further role than the setting in motion of purely mechanical phenomena which we group under the title of 'transmission'. The displacements of the fluid in the scalae would not lead to any sensation unless they transmitted their energy to an organ specialized for the transformation of mechanical energy into a nerve impulse. This occurs in the organ of Corti, which is to be found in the innermost part of the cochlea, in the cochlear duct filled with the endolymph. Situated between Reissner's membrane and the basilar membrane which supports it, the organ of Corti (fig. 5) is made up of ciliated sensory cells which are surrounded by groups of other supporting cells. The organ is kept in place by two rigid pillars, the 'pillars of Corti', which are separated from each other at the base but meet at the top to enclose the 'tunnel of Corti'. These cells are arranged on one side and the other of the tunnel. On the inside, there is one row of cells called 'inner-hair cells', and on the outer face of the tunnel from three to five rows of 'outer-hair cells'.[11] The cilia, which arise from the upper pole of the cells, are in close contact with a membrane which covers them and which is called the 'membrana tectoria'.

## *Travelling waves and electrical phenomena*

When the foot of the stapes transmits the sound waves to the fluids in the labyrinth, the basilar membrane moves under the influence of the waves in the liquid. But the displacements of this membrane occur in a certain direction and appear in the form of waves which originate at the base and pass up towards the top, as Bekesy was able to show with the aid of a model of the cochlea (fig. 3). As they move, these 'travelling waves' cause a very typical deformation of the membrane. This increases in amplitude as it leaves the base, reaches its maximum at a certain point, only to disappear immediately afterwards.[12] The zone of maximum amplitude of the wave depends on the frequency of the stimulus and on the local resonance in the membrane itself. When the sound is high-pitched it is situated



5000
2000
1000
7000
600
20,000 Hz
mean width
0·21 mm at the base of the spiral
0·34 mm in the middle of the spiral
0·36 mm at the apex of the spiral
length 32 mm

*Fig. 4. The localization of frequencies (Hz) in the cochlea as a function of the width (in mm) of the basilar membrane. (After O. Stuhlman, Jr,* An Introduction to Biophysics, *John Wiley and Sons, Inc.).*

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(10) *The basilar membrane is about 32 mm long. It becomes wider as it passes from the base to the summit (fig. 4).*

(11) *The inner hair cells number about 3,500 in one row and they are about 12 microns in diameter. The outer hair cells number 20,000 to 25,000, have a diameter of about 8 microns and are arranged in five rows at the top, four rows in the middle, and three rows near the fenestrae.*

(12) *The speed with which the wave moves is about 1·6 feet per second at the top.*

(13) *The currents which give the 'microphonic effect' (alternating currents) originate in the outer hair cells by a transverse movement of the cilia in relation to the long axis of the cochlea. The inner hair cells give rise to a different type of electrical response, the negative 'summation current' (direct current), by a longitudinal displacement of their cilia (Davis).*

so much nearer the base, when the sound is lower, it is nearer the top. It is therefore possible to draw a map of the localization of frequencies along the whole cochlea (fig. 4).

All these data, and in fact most of the work that has been carried out on the mechanism of the cochlea, depend on the remarkable electrical characteristics of the organ. The resting current, as measured in the endolymph, is +80 mV to +100 mV in relation to the perilymph (Bekesy). This resting current seems to have its source in the stria vascularis (Davis). On the other hand, if an electrode is inserted by a very delicate technique into one of the sensory cells, the resting potential is found to be −20 to −60 mV.

An electrode placed on the fenestra rotunda, for example, will register an alternating current when a sound is being heard by the animal under examination. This phenomenon, discovered in 1930 by Wever and Bray, is called the 'microphonic effect' of the cochlea and it allows us to reproduce electrically the shape of the stimulating sound wave in the same way as would a microphone placed in the path of the sound waves.

This electrical response of the cochlea is due to the displacement in an appropriate direction[13] of the cilia of the sensory cells in contact with the membrana tectoria, when the basilar membrane responds to the waves. The change from 'transmission' of sound to its 'perception' occurs in the ciliated cells, which have the task of initiating the nerve impulse in the fibres of the cochlear nerve originating around their bases. It is still not known, however, if the nerve fibres are excited directly by the electric current (ephasis) or through the action of a chemical mediator, such as acetylcholine (synapsis). In any case, it is only the impulses in the nerve fibres that can stimulate the brain, the seat of the sensation.

## *Theories of hearing*

The way in which the auditory system as a whole may work has been debated for a long time. Among the best-known theories we must mention the resonance theory of Helmholtz (1867), according to which the analysis of sounds takes place in the sensory organ itself, the cochlea; and the telephonic theory of Rutherford (1880), according to which the analysis takes place in the brain. Modern data obtained by neurophysiological techniques have led Wever and Bray to consider nervous conduction in the auditory nerve in a very particular way. It is well known that the 'refractory period' of a nerve fibre prevents it from becoming completely excitable again for a certain period after a stimulus, although this period is very short. This would not be compatible with the known possibilities of hearing a sound with a frequency of 20,000 cycles a second. However, it has been found that although a fibre of the cochlear nerve may respond in rapid succession to low frequencies of a few hundred cycles, and then to higher ones, it transmits only impulses which are a sub-multiple of the frequency of stimulation. But, in parallel with this slowing of the rate for a fibre, other nerve fibres are brought into action which, working together, carry a total of information which corresponds to the frequency of stimulation. This 'volley-theory' has been put forward appropriately to enable us to get over the difficulty inherent in the nerve fibre's limitations in the transmission of frequencies by the auditory nerve.

## *The central pathways of hearing*

The nerve impulses follow the fibres of the auditory nerve as far as the brain, travelling at a speed of some 98 feet per second. This pathway is divided into sections, each forming a relay of 'neurones'. Leaving the cochlea, the fibres reach the cerebral cortex after passing through the brain-stem and the thalamus in the course of a long and complex route, at certain points on which it has been possible to find a localization of high and low frequencies. One of the important consequences of synaptic relays[14] thus created is that there is a spreading out in the time of the nervous conduction from the periphery to the centres.[15]

In any case, not all these fibres run to the auditory area; a certain number enter into the constitution of 'associative' circuits at the origin of reflexes that function without cortical intervention.[16] Nevertheless, the final destination of the majority[17] of these fibres is a part of the temporal cortex situated at the bottom of the Sylvian fissure, called the 'auditory area'.[18] This area receives impulses from both cochleae as a result of the crossing over of some of the fibres. It is at this level that the sounds finally take on their psychological character and become sensations.

This schematic description gives one a glimpse of the complicated process of hearing. Although many painstaking researches have already enabled us to answer some of the questions, there are still many that remain to be elucidated. Studies on acoustics, on neurophysiology, and on psychophysiology are all concerned with our efforts to understand exactly how we hear.

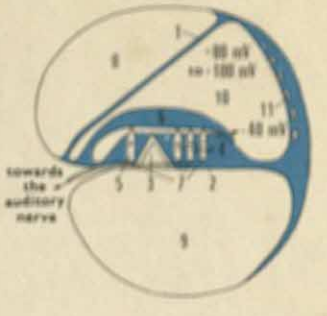

*Fig. 5. Diagram of a section of a turn of the cochlea spiral. (1) Reissner's membrane; (2) basilar membrane; (3) tunnel of Corti; (4) outer hair cells; (5) inner hair cells; (6) membrana tectoria; (7) nerve fibres; (8) scala vestibuli; (9) scala tympani; (10) cochlear duct; (11) stria vascularis. (After H. O. Davis).*

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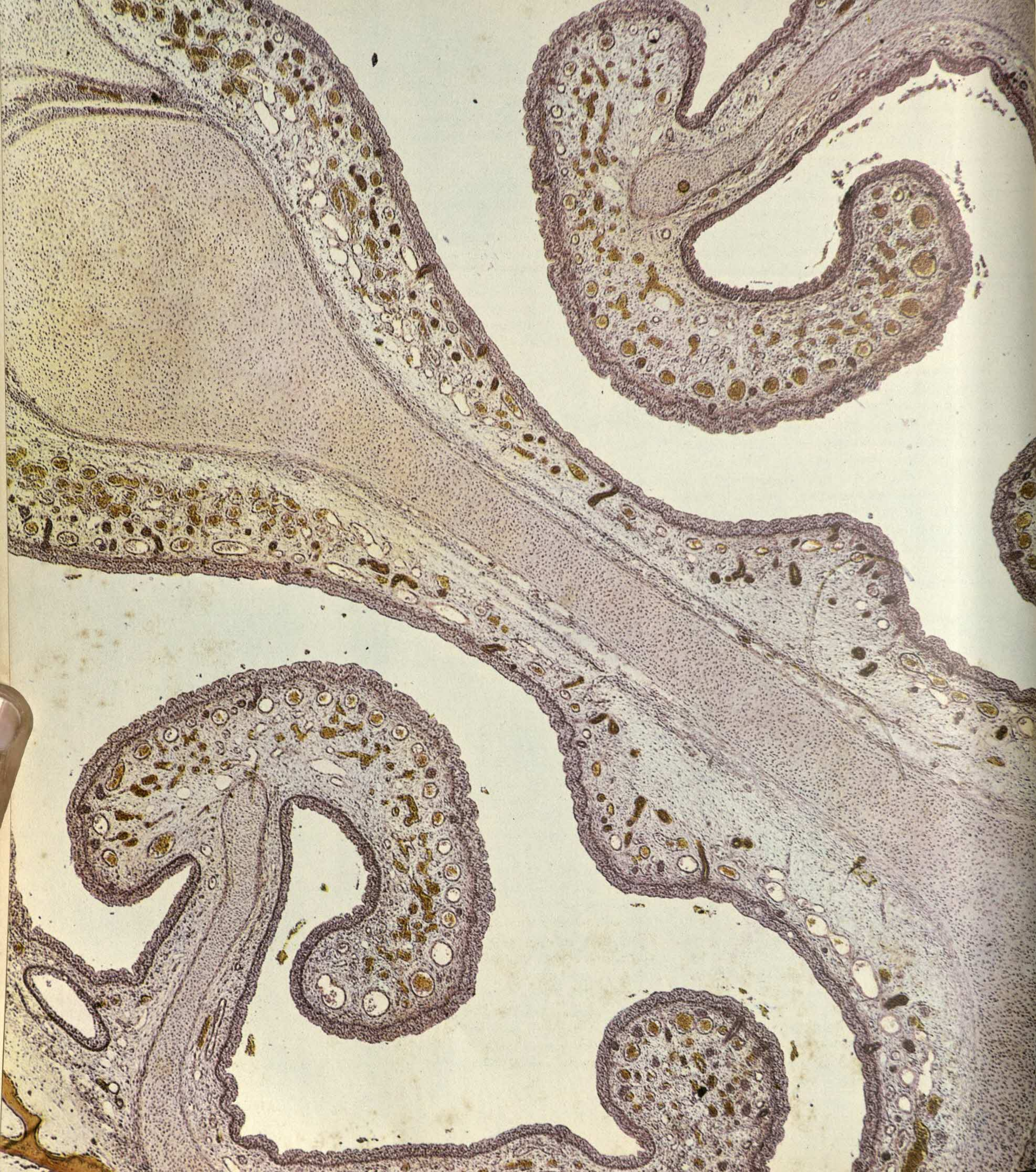
(14) *A synapse is the point of junction between two neurones. Each synapse leads to a delay of about 0·6 milliseconds in the transmission of the nerve impulse.*

(15) *The latent period is about 1 millisecond in the bulbal zone, 4·5 milliseconds at the level of the corpora quadrigemina, and 5 milliseconds in the internal geniculate body.*

(16) *Among these reflexes we may mention those which cause movements of the eyes, the head, and even the whole body, those which cause contraction of the muscles of the middle ear, and those which lead to involuntary nervous activity.*

(17) *The* temporal cortex *does not receive all the inflow from the two cochleae. If one auditory area is removed from an animal, this leads to a loss of hearing of only about 2–5 dB; the removal of one auditory area and one cochlea to a loss of 15 dB, and the removal of both auditory areas to a loss of about 70–75 dB.*

(18) *The* auditory cortex *is in reality made up of three zones in close contact. They are the principal auditory area, the secondary auditory area, and the associative auditory area.*



# The sense of smell

### *Marcel GUILLOT*

*The French psychophysiologist, Henri Piéron has made the happy suggestion that sensations should be looked upon as a 'guide to life'. This expression seems very appropriate, because a crude sensation not only brings man a direct message from the outside world and tells him about what is going on there, but also sets in motion a mysterious cerebral process that transforms the message by associating it with what has been learnt before, and enables him to draw conclusions which appear to go well beyond the obvious content of the message received.*

In the case of hearing and sight this association is quite clear, but it is less so perhaps in the case of smell, with which we are concerned here. The first question is whether everyone who is in contact with a certain substance that has a smell in fact perceives the *same* smell. Some may appear to like it, others to find it nauseating. It would therefore be tempting to conclude that sensory behaviour varies a good deal from one person to another.

In reality, however, it appears that with very rare exceptions, to which we shall return later, the actual sensation of smell is the same for everyone who comes into contact with an odorous substance (for example, a plant essence such as oil of jasmine). If some 'like' the smell and others 'dislike' it, the reason is, as we have said, that the crude sensation is always accompanied by a psychological change which connects it with past memories, often of an affective or emotional kind. The classic example is that of oil of cloves. In a small concentration with other odorous elements, this oil can be used as the basis of a 'carnation' perfume, and in the usual small quantities the smell is pleasant to most people. But if someone has once been treated with oil of cloves at the dentist's during a filling, he may well have a very disagreeable memory of the substance and will avoid contact with it, especially in the form of spice in cooking. If he happens to smell a perfume containing a small quantity of oil of cloves, one of two things may happen: either he will not notice anything except the carnation perfume and will enjoy it, or he will perceive the underlying smell of cloves, and the memory of the dentist's treatment will cause him to find the perfume thoroughly repugnant.

Cases of this sort are innumerable. Each time a human being comes into contact with a smell, the sensation is at once linked up with a multitude of olfactory memories which may be more or less conscious and either recent or distant in time, and all associated with precise facts. This means that sensations of smell, like

*Opposite page: transverse section of the nasal fossa. The cartilaginous folds, covered by a mucous membrane, can be seen. Embedded in these are the olfactory sensory cells. (Mag. × 70. Photo Lod).*

other sensations, have an influence on our behaviour by bringing into play phenomena of association that are often difficult to elucidate. Sometimes, indeed, a true conditioning seems to occur and examples have been known of men and women who can retain their physiological equilibrium or execute certain acts only when a kind of inhibition has been lifted by a particular smell. This can be true of sleep, of appetite, or even of certain kinds of behaviour.[1] The correlation between smell and sexual phenomena is even more complex.

I myself have been particularly concerned with identifying certain odorous molecules (very rare, in fact) which have the property of causing *qualitative*, as well as quantitative, differences in sensation between one person and another. Up to now, the only two substances known by me to have this property are androstane-3-one and $\Delta$-16-androstene-3-ol. These two synthetic compounds are perceived by about one third of the population as possessing an *animal* odour which is most unpleasant, indeed, scarcely bearable, whereas another third perceive it as a very pleasant *floral* or fruity perfume, like musk or the smell of a peach or a strawberry; for the last third (very approximately), the substances have no perceptible smell. It is curious that the two substances should act independently of each other (ie, that one person may fall into the first category as regards one of the substances and into the second or third category as regards the other, all combinations being possible). From this fact, in relation solely to these two odorous molecules, it is clear that the possible number of types of human behaviour is a fairly large one: at least six or seven distinct categories appear to exist.

But there is more to it than this. If the person is a woman, the result of the test will differ according to whether she is having a menstrual period or not. The very nature of the sensation changes in this cyclical fashion, qualitatively as well as quantitatively, and the only explanation that can be given is that the nature of the olfactory message received depends on the hormonal state of the subject. This appears the more likely, as the structure of the two molecules in question is very close to that of the sex hormones. In fact, the basic molecular structure of these substances forms the skeleton of that of the hormones, and therefore pure coincidence in these effects is most improbable. The likelihood of this association is reinforced by the fact that also during pregnancy the type of perception changes, and by the fact that men tested at an interval of several years before and after puberty also show a change.[2]

## Perfumes and hormones

Phenomena similar to those involving artificial odorous substances occur in nature. It is well known that if a dog is attracted to a bitch on heat, it is because the latter produces certain odorous chemicals which are carried in the air and reach the olfactory mucosa of the dog. The fact that the dog immediately finds itself in a particular physiological state shows that this odorous substance has acted as a hormone, in this case as a hormone which can be carried from one living being to another some distance away.

It might be said about cases of this sort that perfumes are 'aerial hormones'. It is only in certain cases, however, when an adult man experiences violent emotions, that he is at all conscious of being vigorously affected by such olfactory stimuli. Most of the time he thinks very little about them, the only reactions which are familiar to him being affective reactions of attraction or repulsion, especially in the case of culinary smells. One notices constantly how appetite can be stimulated by certain smells or put off by others.

It is clear, however, that young children, much more than adults, are influenced by olfactory impressions. Writers wishing to recall traces of their behaviour as children, often mention that when they were quite young they found it natural to characterize each garden they played in, each house, and even particular rooms in each house, and each person they met, by specific smells. It seems that from the moment we become capable, as adults, of constructing a picture of the world around us, it is based almost entirely on visual data, and we neglect our olfactory faculties and memories and allow them to perish. But dogs seem to rely on their sense of smell all through their lives as their principal 'guide to life'. Their olfactory memory is excellent and their ability to discriminate is such that at the first smell they are capable of recognizing the trace of any person or of an object belonging to that person.[3]

This is all the more mysterious because the human body has not just one smell; moreover, the smell of the hair, the armpits, the hands, and so on, seem to have nothing in common. If this is so, how can a person be characterized by *one* 'specific' smell? No other explanation, however, can be offered to account for the facts observed (notably by Kalmus) in the dog.

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(1) *It is known that some smells can cause asthmatic paroxysms in sensitized persons, and it appears that these smells produce their effect not only by the direct action of the substance on the respiratory apparatus, leading to an allergic reaction, but also by indirect action through an olfactory sensation.*

(2) *This connects with the importance of the association of ideas which is often established between the memory of a certain smell and a physiological mechanism. There have been cases in which a man, having once loved a woman who used a certain perfume, was incapable of experiencing sexual desire unless he smelt the same perfume again.*

(3) *Hans Kalmus has shown that among the most remarkable of these animals discrimination failed only in the case of identical twins. Only in this case was there a lack of certainty, so the 'specific' smell of the two was probably the same.*

These psychophysiological characteristics of smell in general seem of much more interest than the purely scientific ones of the mechanism of smell. For a long time it was thought that this mechanism was something quite mysterious. It was believed that odorous substances acted at a distance by emitting material 'particles' of a special nature, or else sent out 'rays' of a kind as yet unsuspected.

## *The mechanism of smelling*

More recently, these fantastic hypotheses have been modified. Evidence shows that the distant action of an odorous substance on our olfactory mucosa is produced very simply by molecules passing through the air, having become detached from the surface of the active substance. They are carried from it either by diffusion or by air currents, until they reach the sensory cells in our noses. Thus we can see why sniffing is important in attempting to perceive a smell, and also why there is a relation between the volatility of a substance and its capability of being smelt. I have myself been able to show that a molecule which has no centre of symmetry (and can therefore exist in two isomeric forms[4] which turn the plane of polarized light in opposite directions), generally has a biological action that is very unequal for the two isomers (although the chemical constitution, except for the symmetry, is identical in both molecules), and also, that when this structural disposition exists for an odorous molecule, the two forms—'right' and 'left'—though having the same smell, and the same volatility, are unequally odorous.

In certain cases, it even seems that when an optically active substance, which also has a smell, acts at the same time on several olfactory receptors, there is a difference in the quality of the smell as a function of the molecular dissymmetry, as well as a difference in intensity. This can be explained only in terms of a direct contact between the odorous molecule and the sensory receptor organ, proving definitely that sensation occurs at the same time as contact, ie, at the moment when the molecules carried in the air are captured by the sensitive surface of the sensory cell.

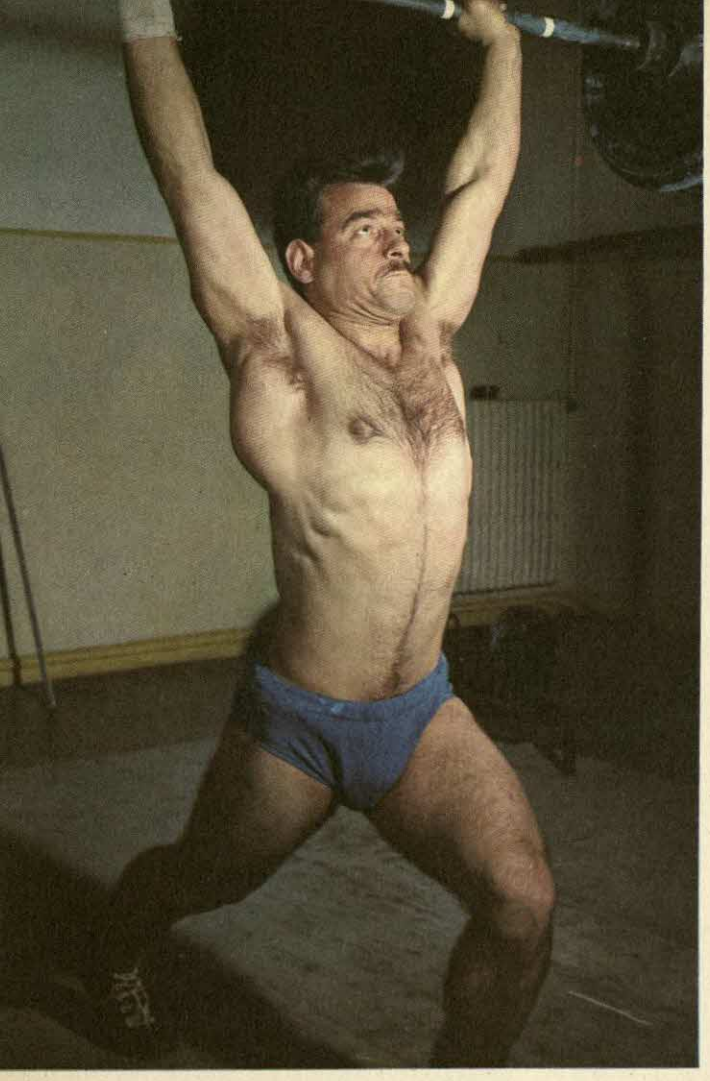
The part played by the sensory organs themselves is as yet imperfectly understood. Everything appears to show that certain smells are perceived by specific receptors. It seems impossible to deny this, especially if one looks into the question of specific anosmias.[5] Some people find that hydrocyanic acid smells of bitter almonds, but many others can detect no such smell. By analogy with what happens in certain anomalies of taste, it seems probable that for certain substances the threshold of sensitivity must vary very much from person to person. In those with high thresholds, the smell of hydrocyanic acid would not be perceived until the concentration in the air rose to a high level, though in fact this cannot be proved by experiment because hydrocyanic acid is too toxic. Whatever the explanation may be, the fact remains that, for one person there is an anosmia, or at least an almost complete lack of sensitivity to *one* smell, yet all the others are normally perceived by him with great sensitivity, indicating that in this case a special mechanism must come into play. Whether this mechanism is absolutely specific or not is irrelevant.

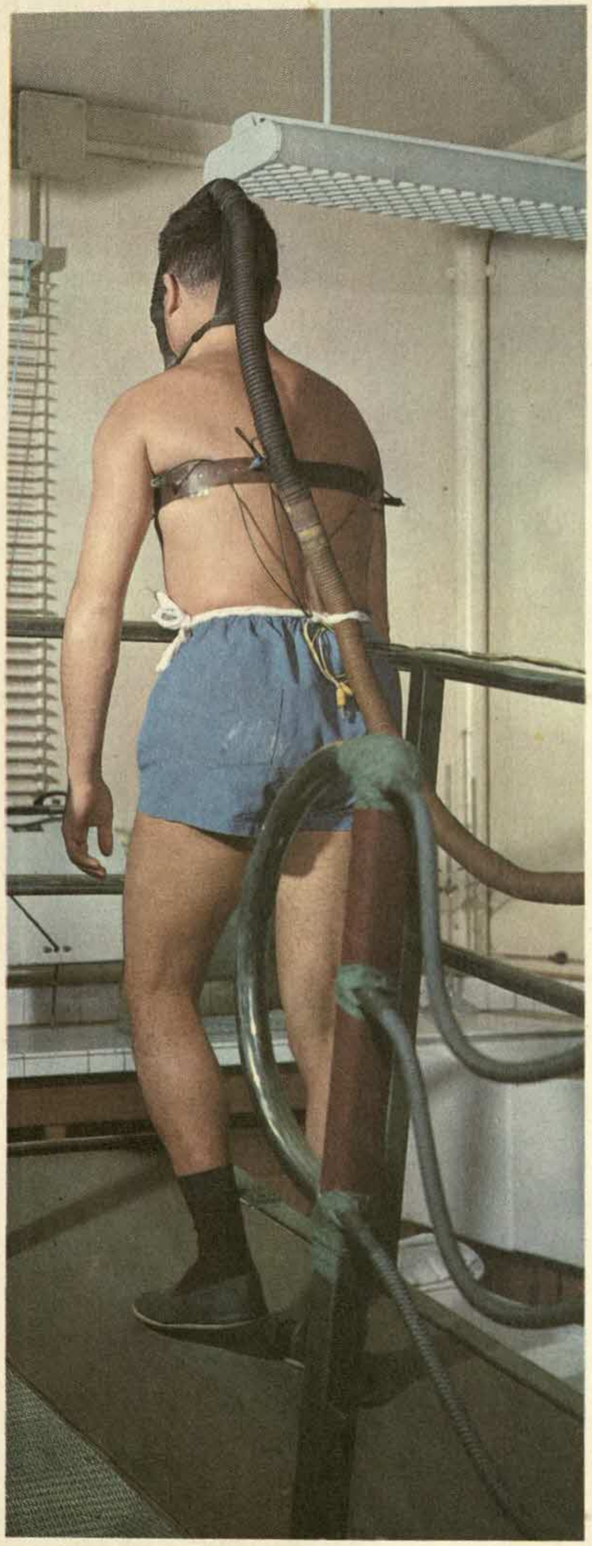
In other cases it is clear that certain smells affect several receptor organs at the same time and that a small change in the molecular structure of the substance has an influence only on the proportion in which the different receptors are affected. This conception, put forward by Lord Adrian, is certainly valid in most cases. A molecule of a substance with a smell would act on the human olfactory mucosa as a whole, affecting two, three, four, or even as many as ten, specific receptors, and each of them with a certain probability. A concerted effect would result which would determine the particular character of the sensation. This is reminiscent of the trichromatic theory of vision, but in this case we cannot consider just three or four types of receptor. For the sense of smell it is necessary to allow for a much greater number. The total number of sensory cells in the olfactory mucosa has been calculated: there are about a million, of which some are apparently 'specific' (several dozen types, perhaps), the others being 'non-specific' and so corresponding to the case in which a substance affects several receptors (there might be also several dozen types of these). To sum up, it would be in either case the distribution of the sensitive points on the mucosa which would determine the quality of the smell; but the 'telephone exchange' to which all the cells are connected, and which elaborates the messages that are sent to the cortex, appears to be so complex that unfortunately we are as yet unable to investigate it experimentally. For this reason, the psychophysiological studies which we can undertake on the sense of smell have at least as much interest as physiological and biophysical studies aimed at elucidating the sensory mechanisms themselves, which are as yet out of range.

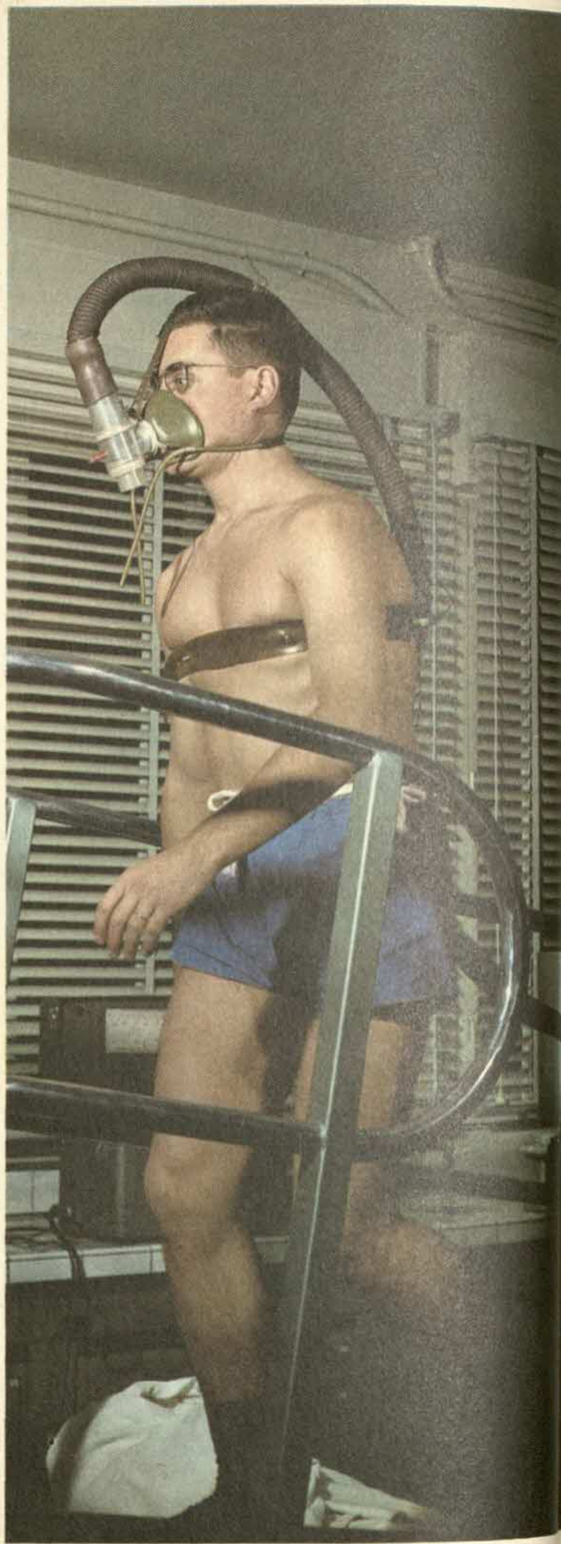
(4) Isomers: *substances of which the molecule is formed of the same atoms in the same numbers, but arranged in different ways in relation to each other, resulting in properties equally different for the two molecules.*

(5) Anosmia: *absence of the sense of smell.* Specific anosmia: *a disability which renders a person incapable of perceiving the smell of some particular substance, although he can smell others normally.*

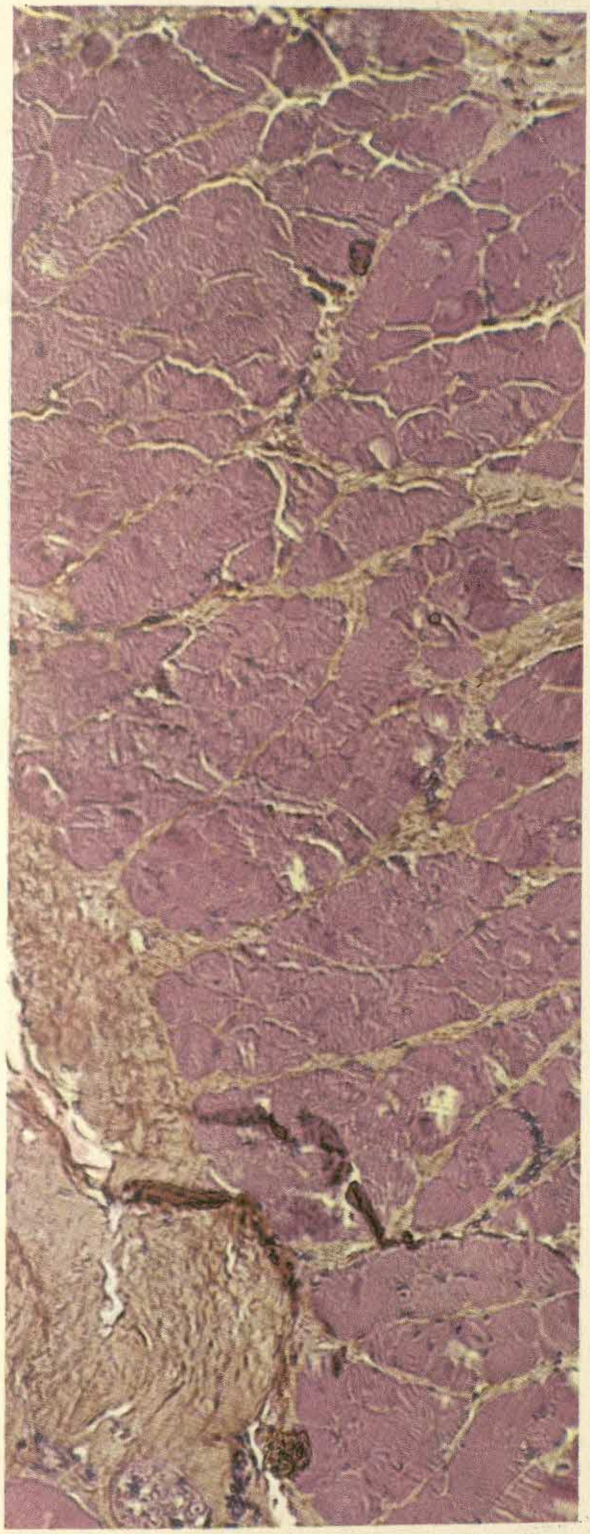
# Muscles and muscular effort



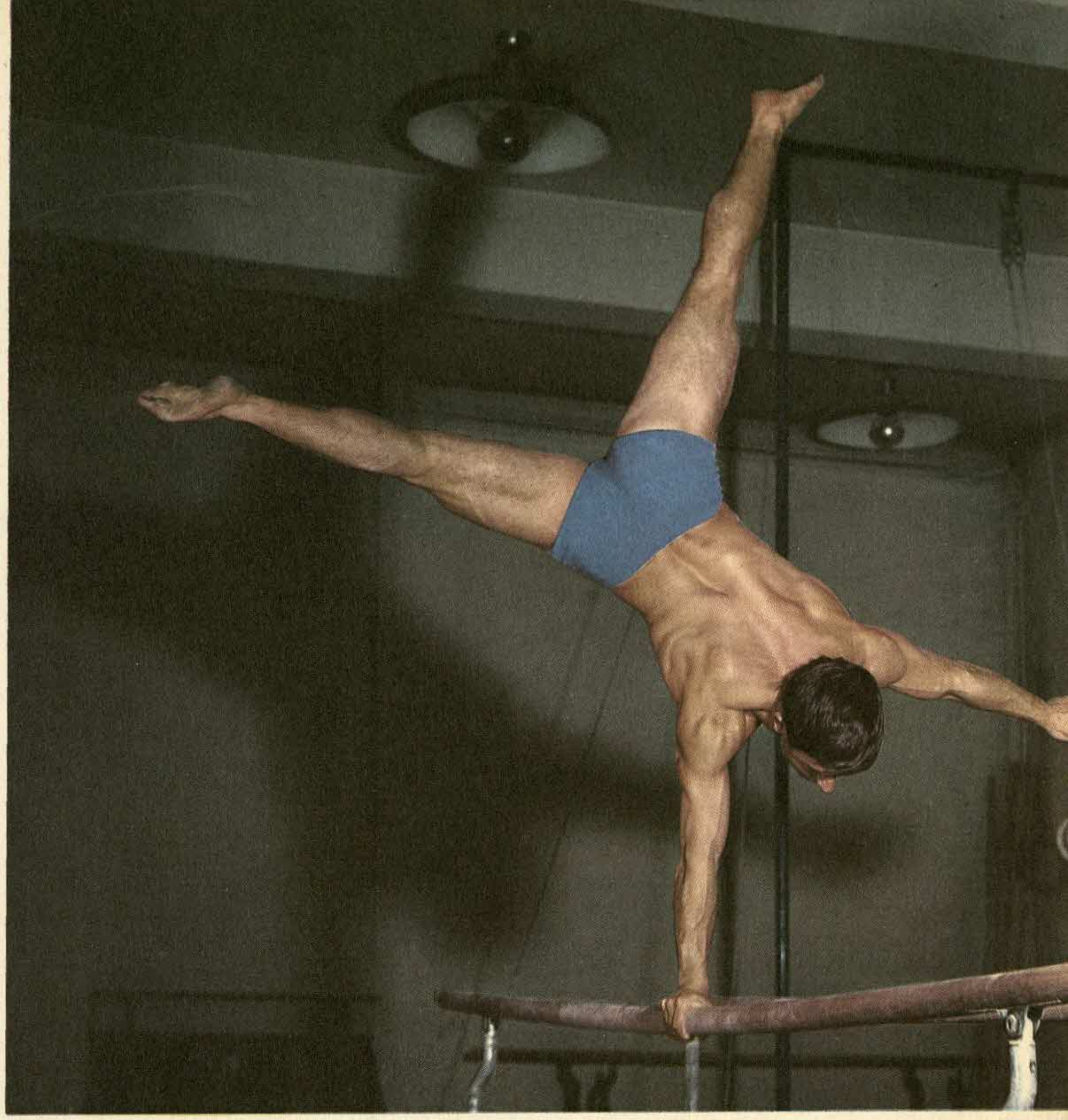


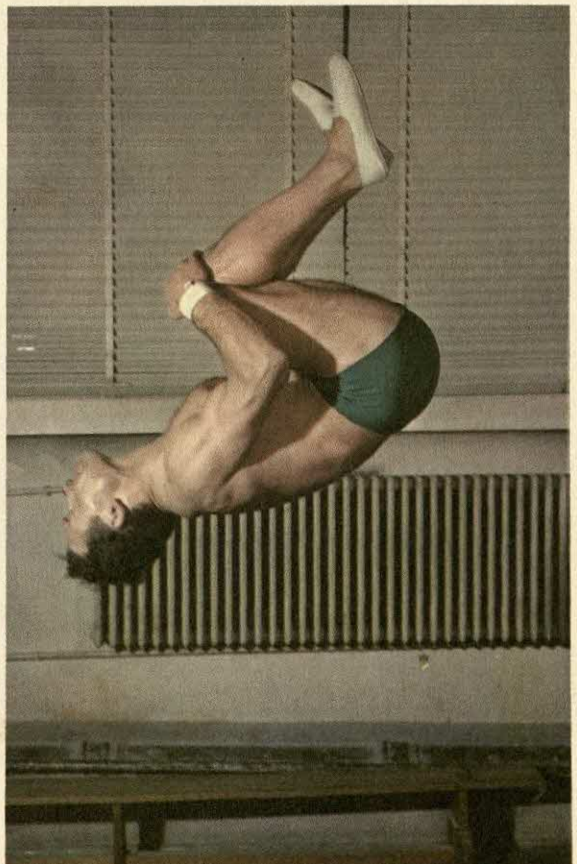


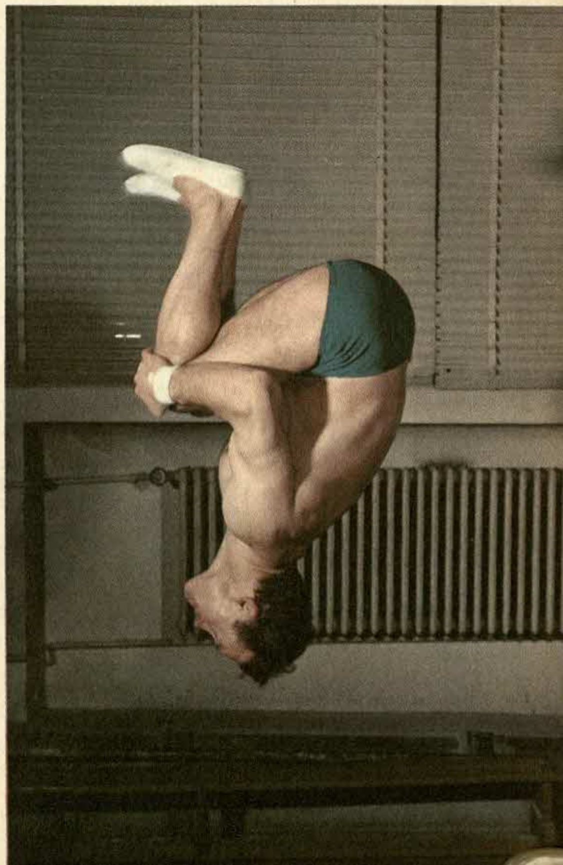
*The muscle, the 'chemical engine' of the human machine, performs work which is easily measured. Above: at the French Study and Research Centre for Aeronautic Medicine, a subject carries out a physiological experiment. He walks on a moving platform and the increase in respiratory output is measured by collecting the expired air in a mask provided with a valve. It is thus possible to estimate the muscular work involved. To the left, and on the right-hand page are athletes doing various types of exercise which bring a particular series of muscles into play.*



*Above, right: the deltoid, trapezius and latissimus dorsi muscles are particularly prominent; they prevent the body turning at the shoulder. Above: transverse section of a striated muscle under the microscope, showing the bundles of muscle fibres. (Photos Lod. Those of the athletes were taken at the French National Institute of Athletic Sports).*







# Muscle, a chemical engine

Alexandre MONNIER

*Because of its relatively great mass, the muscular system has been a favourite subject of study for both biochemists and physiologists. The chemical compounds which are produced by muscular contraction are, in fact, so plentiful that their analysis is relatively easy. Muscle is therefore the best understood of living tissues, both in its fundamental characteristics, which it shares with all other tissues, and in its own particular function, namely the transformation of chemical into mechanical energy.*

We are scarcely a century distant from the time when almost all the mechanical energy available to man came from his own muscles and from those of the animals he had been able to domesticate. The non-muscular energy that he was able to make use of, thanks to such apparatus as the watermill and the windmill, was minimal, except at sea, where large sailing ships, with deep keels, were able to beat almost into the wind. Up to that time, the only boats that could battle into the wind were galleys manned by galley-slaves chained to their benches.

## The structure of muscles

Today, man has many sources of energy, far exceeding the dreams of his forefathers. Yet the decline in the use of muscular energy was slow. Not much more than fifty years ago, six hundred thousand horses were in harness in the streets of Paris. Muscular energy is no longer as important in industry as it used to be, but nevertheless it remains the subject of much study. In fact, its use in sport of all kinds is looked upon as essential for good health, and as the bulk of muscle makes up nearly half the weight of a man, its proper functioning is clearly important for the health of the other organs as well.

There are two kinds of muscles:

(a) Smooth muscles, such as those in the walls of the blood vessels, of which they regulate the calibre, and in the intestines, which move slowly by their action. The fibres of these muscles are small elongated cells.

(b) Striated muscles. The fibres of these are much larger and consist of a sort of elongated sac, which may be more than 10 cm long and up to 1/20 mm wide. This sac contains not just one nucleus, but a large number. It is what is called a syncytium, and is composed of cells which have merged completely and shared their protoplasmic contents. Inside this sac is the contractile apparatus itself. This appears under the microscope to be made up of a series of parallel striations running perpendicularly to the axis of the fibre. A network of nerves, derived from a motor-nerve fibre, makes contact with each muscle fibre by means of a motor end-plate. When stimulated, either by a nervous impulse or an electrical excitation from outside, the fibre contracts, ie, it suddenly shortens and remains shortened for several tenths of a second. A permanent shortening, or sustained contraction, requires repetition of the nerve impulses or of the electrical stimulation.

Here we shall speak only of the striated muscles, since they provide by far the greater part of the mechanical energy which can be produced by man, ie, that produced by the heart and all the muscles that are attached to the bones that make up the skeleton. Muscular work is accompanied by an acceleration of the respiratory movements which is reflex in origin, stimulated by the muscular activity itself. This changes the oxygen and carbon dioxide content of the blood, the oxygen being diminished and the carbon dioxide increased. These variations cause the excitation of certain neurones in the medulla which regulate the movements of the diaphragm and the muscles of the thoracic cage. Thus pulmonary ventilation responds to the needs imposed by the work of the muscles, to bring oxygen to these muscles, and to rid them of carbon dioxide. Muscles may thus be compared to engines which burn fuel in the same way as the engines of ships, cars, and aeroplanes. The analogy must not be taken any further, however: engines which use petrol or coal are all the more efficient when they are working at a higher temperature (Carnot's principle).

Sustained muscular activity leads to a slight raising of the body temperature (shivering, for example, is a reflex means of combating cold), but the resulting rise is scarcely more than one degree. A single contraction raises the temperature of a muscle a few thousandths of a degree, as A. V. Hill showed by means of extremely sensitive thermo-couples. It should not be thought, however, that the chemical energy is almost entirely transformed by the muscle into mechanical work, ie, with an efficiency approaching 100 per cent. On the contrary, both muscles and efficient car engines have about the same efficiency, which is no more than 25 to 30 per cent. In each case, more than two-thirds of the energy is lost as heat, but at very different temperatures.

## *Fundamental chemical reactions*

What, then, is the muscular fuel which is 'burnt' in this way at a low temperature? It is a sugar, glucose, which is either drawn from the blood which flows through the muscle or provided by the breakdown of a polymerized dehydrated glucose, known as glycogen, and is stored in the muscles, as was discovered by Claude Bernard. Chauveau and Kauffman showed that the blood coming from the muscle which lifts the upper lip of the horse contained less glucose when the animal was eating its meal of oats.

Glucose is not, however, used directly in its raw state. Just as petrol is not used in engines in the same state in which it comes from the ground, so glucose undergoes several changes before it is used. In the case of petrol, the changes are carried out in the oil refinery. In the case of glucose, the active agent is phosphoric acid. This analogy is not so far-fetched as it may seem. In order to turn a certain weekly tonnage of oil into useful fuel, a certain number of workers are needed. The following week they will be available for dealing with the next delivery of oil. In a similar manner, phosphoric acid at the end of a long series of reactions, each accelerated by a specific enzyme, changes glucose into lactic acid and is then free to start the process all over again. It is the lactic acid thus produced which is the fuel for the muscles. But curiously enough, it is not stored up before the work, and burnt during it, like most fuels with which we are familiar. On the contrary, lactic acid is formed *during work* by the muscle and accumulates there (Fletcher and Hopkins). It then disappears slowly *during rest*. It is like a fuel that is used up on account, but in several different ways. About 20 per cent of the lactic acid, after numerous reactions, is in the end oxidized by the oxygen brought to the muscle by the blood. This produces carbon dioxide, which is carried by the blood to the lungs, where it is exhaled. The energy liberated by this oxidation serves all the requirements of the muscle, both for mechanical work and the numerous chemical reactions which require energy. Certain of these reactions lead to reconstitution of glucose, and even of glycogen from the large surplus (80 per cent) of lactic acid formed during the work. Thus the muscle prepares much more fuel than it consumes. The surplus is rebuilt into the original stored substance from which it was drawn (Meyerhof and Hill).

This demonstrates a fundamental principle of modern biochemistry which has been discovered in the course of the study of muscle, that of the 'coupling' of energy-producing and energy-requiring reactions in the same cell. The energy liberated by some reactions allows for the expenditure of those that absorb the energy.

Lactic acid is not the immediate fuel of the muscle. In fact, the muscle can do without it, for a few contractions at least. Lundsgaard showed clearly that if one prevents the formation of lactic acid, the muscle can still contract, but quickly becomes fatigued. (To bring this about, it is enough to put out of action, by means of a specific poison, one enzyme which will cause the reaction essential to the production of lactic acid.) Thus the formation of lactic acid is not the immediate cause of the contraction. The ultimate oxidation of the acid provides only for the reconstitution of the mobilizable chemical energy. The reaction which is immediately 'coupled' with contraction is the dissociation of derivatives of phosphoric acid, either creatine phosphate (P. and G. Eggleton, Fiske and Subbarow), or phosphagen, principally adenosine-triphosphate, ATP (Lohmann and Meyerhof). This dissociation produces phosphoric acid, the role of which in the transformation of glucose into lactic acid has already been mentioned. It also liberates a large amount of energy which can be transferred immediately to the contractile mechanism (Lippmann).

## *The contractile mechanism*

From muscle one can extract a remarkable protein called myosin. If a solution of myosin is made to flow in a narrow stream, the result is a beautiful optical effect called birefringence of flow (J. Edsall and A. de Muralt). Birefringence indicates that the molecules of myosin are very elongated, and this is of course suitable for the formation of muscle fibres.

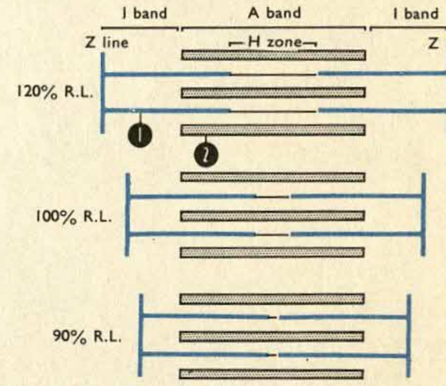
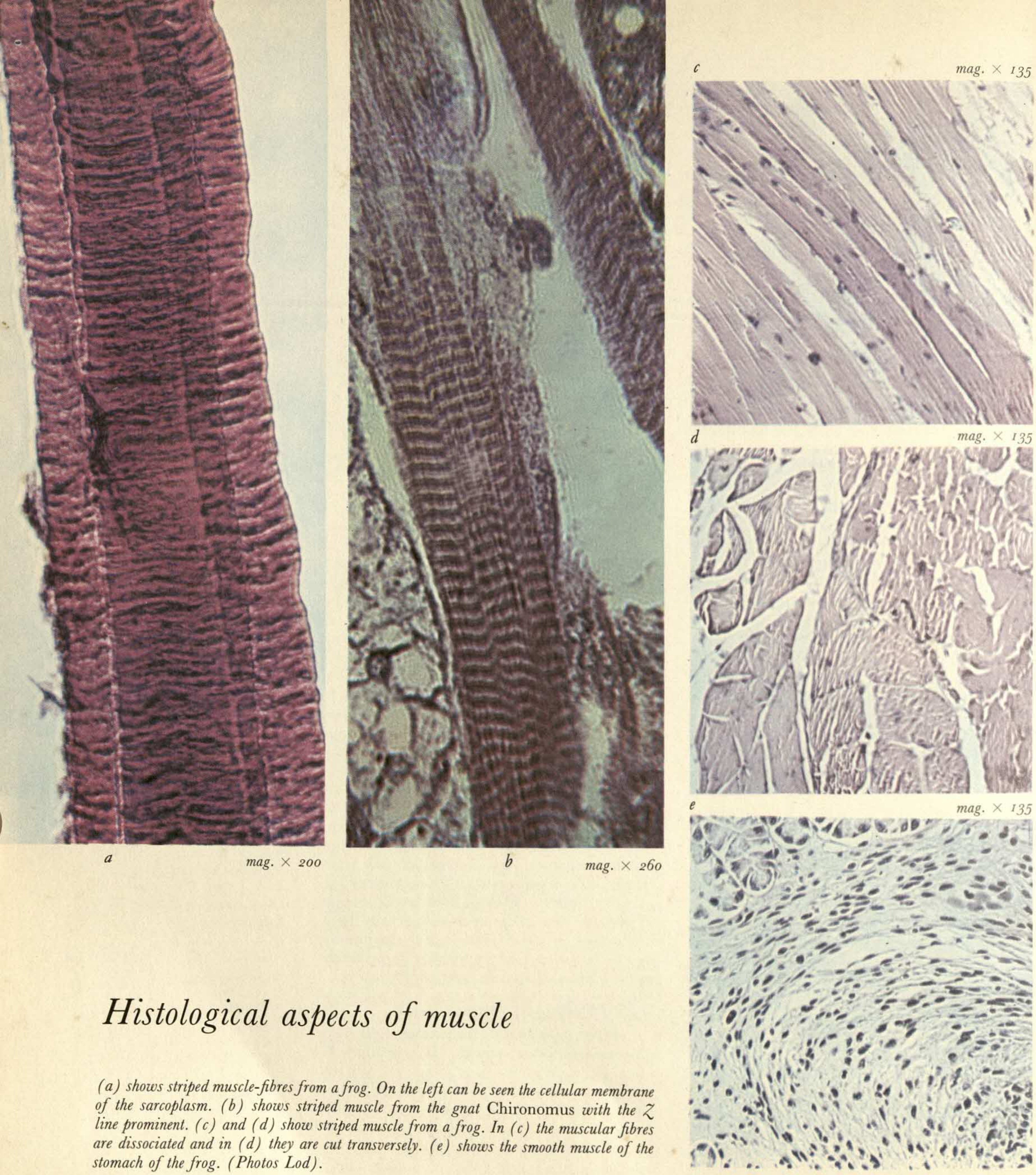


*Fig. 1. Diagram showing the behaviour of filaments of actin (1) and myosin (2) during changes in the length of a muscle. Above, muscle stretched to 120 per cent of its resting length. Below, muscle contracted to 90 per cent of its resting length. The muscle fibres are intersected by a system of regularly repeated bands. The dense, birefringent part is called the A band (or the H zone), and the less dense, non-birefringent part is the I band. The Z line is a sort of membrane dividing the I band into two.*



# *Histological aspects of muscle*

*(a) shows striped muscle-fibres from a frog. On the left can be seen the cellular membrane of the sarcoplasm. (b) shows striped muscle from the gnat* Chironomus *with the Z line prominent. (c) and (d) show striped muscle from a frog. In (c) the muscular fibres are dissociated and in (d) they are cut transversely. (e) shows the smooth muscle of the stomach of the frog. (Photos Lod).*

The birefringence of flow is due to the fact that the molecules of myosin arrange themselves in the stream parallel to each other, as happens when pine logs floating down a river are diverted into a narrow channel leading to a paper-making plant.

A solution of myosin also has another remarkable property: it causes the rapid dissociation of ATP by drawing away from it a molecule of phosphoric acid. Thus myosin is in fact the specific enzyme for the decomposition of ATP (Engelhart and Lubimova). Muscle also contains another protein, actin. A mixture of myosin and actin transforms itself into a new compound, actomyosin, if ATP is added. Thus the energy provided by the dissociation of the latter is coupled to the formation of actomyosin, which takes up energy. But if the mixture of actin and myosin is forced under pressure through a fine spinneret, by a process analogous to that used for obtaining artificial silk, the thread that is obtained will 'contract' actively in the presence of ATP. The spinneret orientates the molecules of actin and myosin in a parallel direction and the actomyosin is formed as a result of a reciprocal attraction of each for the other (Szent-Gyorgyi). The energy liberated by the dissociation of the ATP can thus be partly converted into mechanical energy. The electron microscope has shown that the striation of muscle is a structure formed by two distinct types of parallel filaments, formed respectively of actin and myosin, the ones overlapping the others, so that when contraction occurs they attract each other and interdigitate more closely (H. E. Huxley, J. Hanson) (fig. 1).

Such, in brief outline, are some of the aspects of the chemistry of the muscular mechanism. Other points are also worthy of study, particularly the mechanism of relaxation and the resynthesis of ATP. This latter is believed to take place by means of the phosphoric acid that is liberated by the dissociation of creatine phosphoric acid. It is for the reconstitution of this acid or phosphagen that the energy freed by the slow oxidation of lactic acid, the muscle fuel, must serve. This oxidation, the last stage in the chemistry of the muscle, takes place through the complex cycles of reactions described by Krebs and by Szent-Gyorgyi.

## *Muscle as a reversible chemical motor*

When steam locomotives were in use, the trains which descended the long slopes of the trans-Alpine lines could be slowed down only by the application of the brake-shoes to the wheels, or, at critical moments, by reversing the driving power. These procedures were wasteful of energy, and the electric locomotive has done away with them because electric motors are reversible. When they are rotated by the train running downhill, they act as generators of current and the speed of the train is reduced by feeding the energy so produced back into the electrical circuit.

For a long time it was thought that the internal friction between the protein molecules of muscles, ie, the 'viscosity' of the muscles, was the true limit to the speed of contraction and therefore fixed the maximum that could be achieved in sports and athletics. But if it were, in fact, so, we should need just as much energy to come down a mountain as to climb up it, the effort made during the descent being equivalent to the reversing of a steam engine, and the friction being the same in both cases. However, as we all know, negotiating gentle terrain is child's play compared with climbing. Why is this so? Some recent experiments by Hill have provided the answer. When a contracted muscle is stretched, one can observe very slight variations of temperature on the surface, but these are of reversed sign compared with those seen during contraction. This inversion of temperature-change shows that the stretching of a contracted muscle produces chemical changes which are also the reverse of those found during contraction. Mechanical energy is therefore absorbed and converted into chemical energy. This is what happens when we come down a mountain: the necessary braking is not a wasteful friction, but rather a recuperation within our lightly contracted muscles.

Hill has recently given the Royal Society a striking demonstration of the efficiency of this braking mechanism. Two bicycles mounted on frames had their crank-gears coupled together with a chain. One of the bicycles was pedalled by a champion and the other by a slim young girl. The girl could obviously not withstand the effort of the champion and she had to back-pedal. But when she opposed resistance, ie, when she let her contracted muscles become stretched, the champion tired and very quickly became exhausted.

Thus we are little by little coming to understand the wonderful construction of the muscular engine, and the study of muscle still forms one of the most interesting aspects of general physiology.

# Central control of muscular movement

## *Ragnar GRANIT*

*The models that each age has used in its explanation of the central nervous system have generally been borrowed from sciences other than biology, and in the present era servo-mechanisms and computers are the ones most often chosen. A tolerant attitude towards this method of reasoning is called for, because, after all, the principles laid down in the nervous system are reflected in our thinking and our actions, and if these have led to electronics and computers, something in the design of such instruments is part of our mental equipment.*

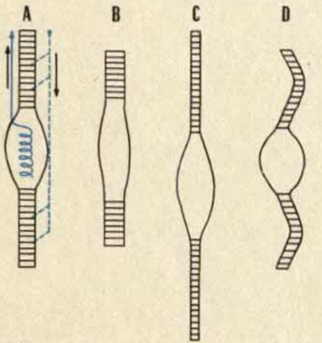


*Fig. 1. Muscle spindle with its capsule. A, the terminal spiral and the afferent nerve (blue line) as well as the afferent motor fibres (blue dotted line) innervate the muscle (striped area) (cf. fig. 5). If A is the initial state, contraction is represented by B: the activation of the afferent motor fibres causes elongation of the capsule and the spiral and, consequently, the emission of efferent impulses (blue line). C the spindle undergoes mechanical traction; the capsule has the same length as in B. D represents the discharge phase of the contracted muscle.*

As, under the guidance of servo-mechanisms, the gun in a ship is aimed at its target, so also our hand, by organized behaviour of a similar nature, is guided to grip a moving object. In both cases there must be recording instruments (sense organs) to measure directional errors, input lines (afferent nerve fibres), one or several controlling stations (nervous centres), output lines (efferent nerve fibres) and feedback control. Together, these form the elements of a circuit, and thus from this point of view the study of the nervous system is a circuit analysis. In our example, the eye follows the target by controlled movements of the eye-muscles which respond to information conveyed to a centre from wave-length detectors in the retina (receptors); across the centre these also influence the muscles of arm and hand. From sense organs in the latter, and in their joints and ligaments, information is continuously fed back to the centres in order to correct deviations and make the movement smooth and efficient. From a desk in front of us, we can pick up objects accurately even when our eyes are closed. Thus we can do much from muscle and joint information alone.

Let us cut an afferent root leading to the spinal cord and record the messages electrically. These, for any single nerve fibre, consist of brief impulses or action potentials, commonly called spikes, which signal information by variations in frequency (not in magnitude) of the individual spike. Thousands of sense organs emit an enormous barrage of impulses which, connected to a loudspeaker, cause a tremendous roar of activity. The task of understanding these activities may seem absolutely hopeless, but painstaking work on single fibres, sampling typical features of activity, is bringing order out of chaos. Fig. 2 is a diagrammatic representation of impulses from two sense organs in the muscle—its so-called muscle spindle, which is placed in parallel with the muscle and hence is silenced when the muscle contracts, and a Golgi-tendon organ, which is in series with the muscle and therefore records every variation of tension caused by stretching or contraction. The spindle records stretch only and hence is a length-measuring device. How clearly the two messages stand out, which without isolation of single fibres would have been uninterpretable. How difficult it would have been to demonstrate the existence of a length-meter and a tension-meter in muscle without taking the trouble to isolate single fibres. Below, we shall return to these two instruments in the muscle.

To begin with, let us consider the difficulties encountered when movement is studied from the central end. Electrical stimulation of the cortical grey matter enveloping the brain (fig. 2) has revealed the existence of a region, called the motor area, from which movements can be elicited. The classic motor area has since been found to be not the only place from which movement can be obtained, but is still held to be responsible for skilled movement and it is now known that sensory afferent projections overlap with the motor area (see fig. 3). There is a definite geographical representation of the body in the motor area and finely controlled movements occupy relatively more space. Even if very highly localized movements can be obtained by fine electrodes and carefully graded stimuli, movement, as we see or record it, is the finished product of many processes and it tells us little about the mechanisms of control responsible for its elaboration. This is the very question in which physiologists are interested and so—hoping for simplification—they have gone down the central axis to the spinal cord and thence to the sense organs in the muscles, to end up with the recording of single fibres and specific circuits.

Imagine the sensory afferents entering the spinal cord through *a* and *b* (in fig. 3). They ultimately find their way to the brain, but also locally, directly or across intercalated neurones, to the *pool of motoneurones* illustrated in the figure. The *a* and *b* fibres overlap widely in their projections and have a convergence zone in common, where their impulses by *summation* can activate the corresponding neurones better than can the individual paths *a* and *b*. The projections have the greatest density on the motoneurones drawn in black and a *fringe zone* of barely activated or even subliminally activated motoneurones is found around it. Let this be the spinal centre of an extensor of the ankle (eg, gastrocnemius). The ankle flexors will have an adjacent pool of motoneurones and if both pools were activated simultaneously, the ensuing movements would antagonize each other because of the antagonistic function of the muscles, one to extend, the other to flex the ankle. More often than not, however, the movement requires that flexors are released when extensors contract, and vice versa. The spinal cord also possesses a corresponding organization connecting the two pools, so that the flexor pool is inhibited when the extensor pool is excited, or vice versa (illustrated in fig. 5). This is the *principle of reciprocal innervation*, as laid down in the spinal segments. The motor area need only, as it were, throw the right switch, for reciprocal or simultaneous action of a pair of muscular antagonists. The major path at its disposal is the *pyramidal* cortico-spinal path, whose fibres cross in the neck, so that the left half of the brain innervates and moves the right side, and the right half the left.

Excitation and inhibition are thus played out against each other on the individual motoneurones, as if they were two processes of opposite algebraic signs, and, indeed, so they are. Fig. 4 shows a motoneurone (black) and its axon (motor fibre) running downwards. On the right is a microcapillary, whose tip, less than half a thousandth of a mm, connects the fluid of the capillary with the inside of the motoneurone as soon as the latter is penetrated, a process shown in its incipient stage on the left. Thus, with the aid of the microcapillary the potential across the cell-membrane can be recorded. Excitation appears as depolarization, inhibition as repolarization. The net depolarizing current or *depolarizing pressure* is directly proportional to impulse frequency.

The best analyzed controlled movements are those concerned with postural tone, by which is meant the adjustment of reflex tension to the state of balance necessary for the execution of movement. Slower adjustments of tone therefore precede rapid phasic action. Let us consider the circuit responsible for adjustments of tone. It is shown diagrammatically in fig. 5 (see also fig. 1). The muscle shown diagrammatically is supposed to be a knee extensor with its length-measuring device, the muscle spindle (fig. 1). Gravity acting upon the body tends to bend the knee; the knee extensors, together with their spindles, are thereby stretched (fig. 1). This forces the latter to discharge afferent impulses (fig. 2) which run directly to the extensor motoneurones of the spinal cord. Their depolarizing pressure will be decreased and consequently efferent impulses are discharged, forcing the knee extensors to contract so as to counteract gravity. Thereby, the load is taken off the muscle spindle, which slackens (fig. 1) until a state of equilibrium is reached between length of spindle and length of contracting main muscle. This illustrates the principle of

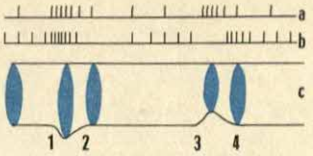


*Fig. 2. Impulses recorded as in fig. 5 (red circuit) from an afferent fibre to a muscle spindle (below) and to a Golgi organ (above), while the muscle undergoes various modifications. Initially, it is of normal length: in 1, elongation: the two proprioceptive organs are discharged; in 2, it returns to normal size and the two organs are temporarily quiescent; in 3, contraction: the spindle mounted in parallel with the muscle (fig. 5) discharges and the Golgi organ reacts to the pressure and sends out an impulse; in 4, the muscle returns to rest: the spindle, briefly elongated, discharges. The Golgi organ remains inert. Spindle and body then return to their normal discharge rhythm.*

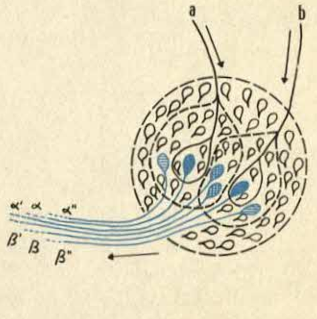


*Fig. 3. The motor cells of the cord of the medulla send afferent axons or fibres (α β) to a muscle forming a motor neurone reserve. Afferent impulses arrive at* a *and* b. *The large circles show partial overlap. The density of projection and overlap, due to convergence, determines the activation or marginalization of the neurones.*

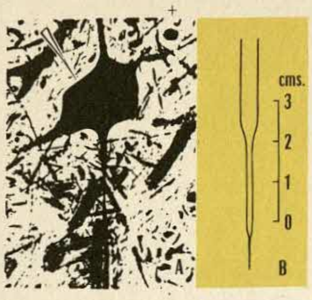


*Fig. 4. Microphotograph of a medullary motor neurone, showing the axon root leading to the muscle. The micro-electrode is shown to scale (capillary tube filled with fluid) ready to penetrate the cell. Inset, the body of the micro-capillary tube.*

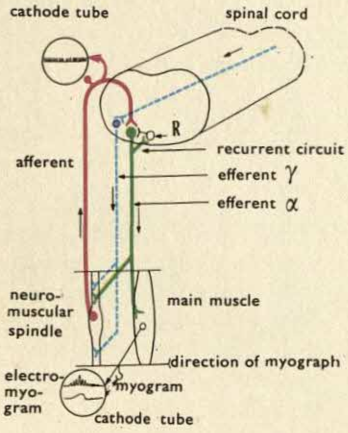


*Fig. 5. Diagram of a control circuit of active muscle tonus (orthostatic reflex). From the spindle, impulses (red) go to the motor region of the medulla. The alpha fibres are indicated in green. Some also innervate a portion of the spindle, although these are mainly gamma neurones (blue) which ensure control.*

*negative feedback*, well known in regulation theory. If, for example, it is desired to keep room temperature constant, we use a 'sense organ', the thermometer, and connect it to a source delivering heat in such a fashion that, when the column of mercury has dropped, say, one degree, this source is turned on. The thermometer begins to rise, and so ultimately the heating source is again disconnected. The system, a thermostat control, will oscillate around a mean temperature selected by the occupant.

On this simile, it is obvious that, by choosing different thermometers or having contacts at different levels, the sensitivity of the instrument can be adjusted from several degrees to a small fraction of a degree. In our circuit for control of postural tone, Nature has seen to this by making the sensitivity of the muscle spindle adjustable according to the needs of the movement. This is achieved by special motor fibres (gamma, *blue*) to the muscular poles of the spindles, shown diagrammatically in fig. 5 on a greatly magnified scale. When these are innervated to send down impulses, the muscular poles contract (fig. 1) and the spindle's spiral sense organ is pulled out with its capsule, just as if it had been extended by stretching from outside (fig. 1). Again, the main muscle is compelled to follow suit and contract until its length agrees with spindle length (that is, spiral and capsule of the sense organ, fig. 1).

Fig. 5 also shows that the gamma efferent fibres which control the sensitivity of the spindle can be activated by pathways coming from several places in the brain, the motor area, some tonus centres in the lower brain stem, in the cerebellum, etc. The length at which the spindle is supposed to operate can therefore be set by the organism, differently for different tasks, be it lifting a heavy weight or adjusting the sensitivity of the fingers, say, when one operates under a microscope and with every increase in magnification is compelled to adjust finger movements in proportion. The distal finger muscles are especially richly provided with muscle spindles. These length-measuring instruments are supported by organs in the joints which record angular movement and direction. They are opposed by the Golgi tendon organs (fig. 1) which measure tension and inhibit the extensor motoneurones when tension increases, thereby preventing overshoot.

It is clear, then, that there are two ways in which a movement can be initiated: the motoneurones (alpha efferents of fig. 5) can be mobilized directly by activating, say, the pyramidal or any other path capable of raising their depolarizing pressure, or they can be activated indirectly by means of the gamma efferents for the muscle spindles. It is likely that all slower movements use the indirect route and that in most motor acts some co-adjustment of alpha and gamma motoneurones takes place. There is an alpha route to the spindles (fig. 5) which in this brief presentation must be left out of account.

In the diagram (fig. 5) is also shown a recurrent path from the motoneurone back to the motoneurones. This loop traverses a special cell (R) which serves as a commutator, changing the effect of the alpha spike from excitation (depolarization) to inhibition (repolarization). This means that as soon as an impulse leaves the motoneurones, another runs backwards from the fork to the spinal cord to suppress the depolarizing pressure for some 40-100 milliseconds, thereby stabilizing the discharge frequency to the low values required by the contractile mechanism of the muscles. The R-cell of the recurrent circuit is itself under central control and so the frequency of discharge can be modified by the organism by setting the R-cell to the appropriate level of sensitivity.

Recurrent collaterals are common in all nervous centres and have other important tasks to fulfil besides the stabilization just mentioned. In any pool of motoneurones (or other neurones with a common task) there are gradations of excitability, as is clearly shown in fig. 3. Depolarizing pressure will be lower in the *fringe* (defined above) and so fringe neurones will fire at a lower frequency. Recurrent inhibition has the property of acting in proportion to the rate of discharge of the motoneurones. Therefore, the highly activated neurones which discharge at high frequencies will exert a greater suppressive effect on the fringe neurones than those can exert on the rapidly discharging ones. This mutual recurrent inhibition accordingly serves to limit the number of discharging motoneurones to the well activated ones, while the others are held in reserve. Furthermore, by mutual inhibition, every loss of excitability will take place smoothly rather than abruptly.

Thus 'movement', regarded from the point of view of nervous control, is an exceedingly complicated affair. A general principle seems to be that Nature tends to multiply possibilities of control so that if something goes wrong somewhere a fair amount of compensation is possible.

# Speech

## *Paul LAGET*

*Very many species of animals are capable of producing sounds. The diversity of timbre is almost infinite, the scale of intensity is remarkable. Almost as diverse are the anatomical structures and the physiological mechanisms employed to produce them. In this Babel of cries, noises and songs one must distinguish those which are produced by chance and play no part in the ethology of the species (for example, the buzzing produced by insects in flight), and those which form an integral part of the behaviour of the animal, particularly when they have a role in enabling it to communicate with its fellows.*

This method of communication by means of sounds finds its highest expression in the human race. If one observes and dissects the laryngeal apparatus of man, which is a region situated in the neck at the upper part of the trachea, one cannot help but be impressed by its complexity. It consists of many cartilaginous and bony structures into which are inserted numerous muscles that run close to and across each other and are provided with a relatively large number of nervous connections (fig. 2).

If we are to try to understand the intricate construction of the human larynx, looked upon as an apparatus for the production of sound, it is easiest to start with a simple version such as that found in the lower vertebrates, the batrachia, for example. In fact, the general outlines of this version are similar to those found in all the vertebrates (fig. 1). Anterior and posterior semi-circular muscles meet laterally on two cartilaginous or bony constituents, the arytenoids. Stretched from the base of these, and with variable relations to the muscular bands, are two muscular ribbons, the vocal cords, which are separated by a gap, the glottis. At the sides of the arytenoids are other muscles varying in number and disposition, which tend to give a more or less elliptical shape to the musculo-arytenoid ring by stretching it laterally, the semi-circular muscles then appearing as a sort of sphincter which can be contracted or dilated. In some cases these are also membranous elements in the form of cavities for resonance, and these reinforce the sounds. They are found in many species of frogs, etc, and are called vocal sacs.

In reptiles and birds the anatomical construction remains much the same, but the sound-producing function of the larynx has disappeared. Reptiles are generally dumb, and in birds the sound-producing organ is of a very different kind, formed at the tracheo-bronchial bifurcation. This itself is often complicated in structure and finely organized, especially in those birds known for their song; it is called the syrinx.

Among the mammals, however, the larynx is the sound-producing organ and it presents many modifications and complications. The carnivores and the primates have an anatomical structure and innervation similar to that of man. In the anthropoid apes the poverty, both in timbre and range, of the sounds given out, makes it difficult to use these animals in the experimental study of the

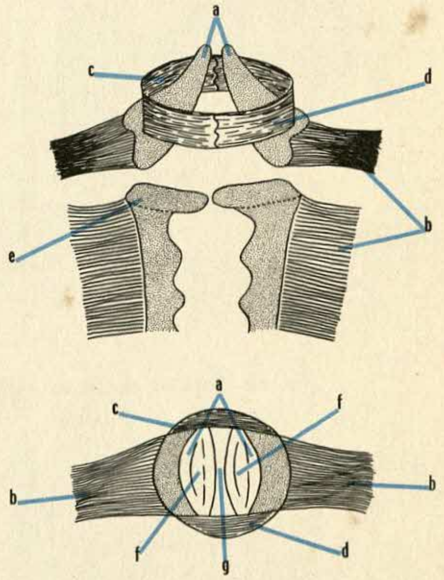


*Fig. 1. A diagrammatic representation of the bony and muscular systems of the larynx of a batrachian, seen from the side (above) and seen from above. (a) arytenoid cartilages; (b) transverse muscular masses; (c) posterior semi-circular muscle; (d) anterior semi-circular muscle; (e) first tracheal ring (which later will become differentiated into the cricoid); (f) vocal cords; (g) glottal opening.*

vocal mechanisms and their comparison with those of man.

The study of the human larynx presents numerous problems, because of both the structure and function of the larynx itself and the peculiarities of the human voice. It is the only type of voice in which one can distinguish sounds of a recognizable pitch or frequency which can be modulated over about two octaves (corresponding to the utterance of vowels and diphthongs), and also a varied assortment of noises—clicking, whistling, etc—which make up the consonants. (These latter are physically related to the sounds of outflow engendered by the passage of expired air through certain narrowings of the air passage above the glottis.) The physiological origin of these two types of sound is different. The consonants are formed in the pharyngo-buccal space by the interplay of the various muscles of the tongue, the cheeks and the lips. The vowels, on the other hand, arise from the passage of the expired air through the larynx, this being modulated to a certain frequency by the vocal cords, which determine pitch. This frequency may be variable even during the utterance of one single vowel in the case of spoken words, or it may remain fixed to a remarkable degree when the voice is in song and the ear can control it accurately. The timbre of the vowels comes essentially from the shape and acoustic properties of the pharyngo-buccal space which lies above the glottis.

This difference in the origin of the consonants and the vowels means that the physiological mechanisms involved in their production are also different. In the case of the consonants, the fundamental problem which has to be considered is how one can produce in rapid succession a whole variety of muscular contractions of which the rhythm and strength are extremely variable, and which together lead to the controlled production of various deformations of the pharyngo-buccal space. It involves, in fact, a voluntary motor action of a very complex type, but at first sight this does not seem to call for any special mechanism or to raise any unique physiological problem.

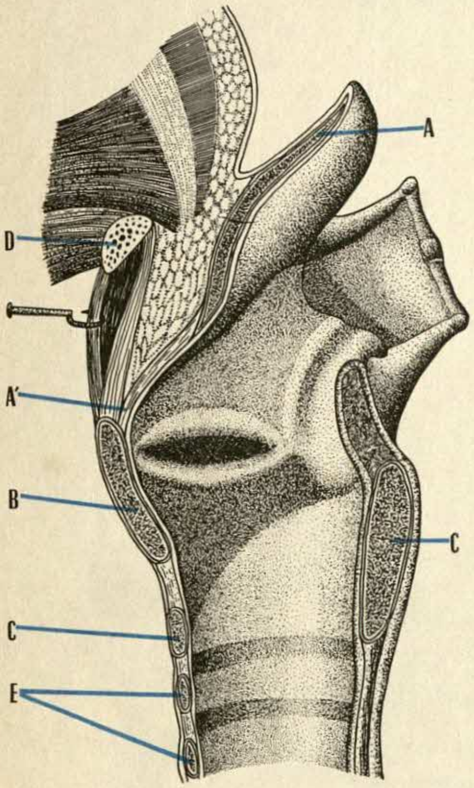


*Fig. 2. Sagittal section of the larynx. A and A' epiglottis and thyro-epiglottal ligament; B. thyroid cartilage; C. cricoid cartilage; D. body of the hyoid bone; E. cartilaginous tracheal ring.*

## *The formation of vocal sounds*

This is not the case, however, when we consider the vocal abilities and, in particular, the production of continuous and perfectly controlled notes by a singer. Since the eighteenth century, the laryngeal mechanisms which make these vocal feats possible have been frequently discussed. Many physiologists and workers on acoustics have attempted to explain the phenomenon by comparison with sounding pipes provided with reeds, as in an organ. According to this theory, the vocal cords are set in motion passively by the current of expired air striking their lower surfaces. The pitch of the sound emitted depends on their tension, which is adjusted by certain muscles called the tensors of the vocal cords. This 'explanation', however, is beset with difficulties and does not account for all the phenomena which have been observed. These are much better explained by the very ingenious theory put forward by R. Husson, which is supported by many experimental findings.

According to Husson, the movements of the vocal cords are not caused passively by the passage of the air, but are due to active contractions produced by nerve impulses which leave the motor centres by the vagus nerve and reach the muscles through the recurrent laryngeal branch. These rhythmical contractions, which occur at a frequency regulated by the subject, open the glottis, each time allowing the escape of a column of air that causes the production of a sound of a frequency equal to the frequency of the glottal openings. Thus the larynx no longer appears to act like a reed instrument, but rather like a siren.[1] This original conception, which refutes the old theory completely, requires that the laryngeal musculature should have properties of rapid response (such as occurs, for example, in the wing muscles of insects, which can contract at very high frequencies), which, though not exceptional are nevertheless rather special. A number of observations involving myography, electromyography, cinematography, histology and electrophysiology have provided solid foundations for Husson's theory, which also has the merit of having led to a considerable amount of research on the structure and function of the vocal muscles. It has been shown, for example, that the structure of the thyro-arytenoid muscles (which essentially make up the vocal cords) is of a particular type. The presence in these muscles of a motor and proprioceptive innervation of exceptional richness shows that the vocal muscles are under a very supple and fine nervous control, and it has also been shown that the vocal cords are highly susceptible to the effect of various hormones. This is especially true of those persons, opera singers and public speakers, for example, who demand much of their larynxes. Such particular sensitivity has led Soulairac to consider the tissue of the vocal cords as a true endocrine effector organ.

(1) Siren: *an apparatus in which the pitch of the sound produced is dependent on the frequency with which a current of air is interrupted.*

# Ageing

*François BOURLIÈRE*

*Once growth has ceased in man and the higher animals (mammals and birds), the organism becomes the seat of a number of qualitative and quantitative changes which are generally called senescence or ageing.*[1] *For a long time this slow and regular atrophy of most of the tissues and organs remains imperceptible and it is only because a whole series of physiological and psychological tests has been devised in recent years that we now recognize its existence.*

It is thought generally that after passing through the growth phase, the organism attains a 'plateau' of relative stability, the adult period in which it is supposed to remain roughly unchanged until finally it sinks into old age through the 'wearing out' of the organs and the insidious progress of many degenerative diseases. We shall see in the following pages that this conception has become less and less tenable, and that old age is, in fact, only the final stage of a slow decline which generally starts shortly after adult stature is reached and sometimes even well before this.

The manifestations of individual ageing can be grouped under two headings: the diminution in the mass of the metabolically active tissues in the organism, and the qualitative changes in structure or in function which occurs in the tissues which remain.

## *The diminution in the mass of tissues*

It has been known for a long time that man 'sinks' as he ages and that at fifty a man is not as tall as he was at twenty. A recent inquiry in France, for example, has shown that men lose on an average 10 cm and women 15·5 cm in height between the ages of twenty-five and eighty-five. Despite a progressive increase in height among European populations in the last half century, the differences noted are certainly of significance. It is known also that many muscles and certain organs, such as the brain, the liver and the kidney, diminish in weight as a person ages. But it is only since we have had methods enabling us to measure the 'active mass'[2] of the tissues taking part in the metabolism of an individual that the extent of this phenomenon has been estimated.

One element, potassium, is found almost entirely in the interior of the body cells (up to 98 per cent of the total). Thus the measurement of the total quantity of this element in the organism at various ages gives us a measure of the total cellular mass and of changes which occur with age. Thanks to the quantitative analysis of a natural isotope, potassium-40, such a measurement is now feasible and was recently made on 1,590 persons of both sexes between birth and eighty years of age. The result is shown in fig. 1. It can be seen that the decline in the total quantity of potassium (and thus of cellular mass) begins at about the age of twenty in men and still earlier in women, and goes on regularly throughout life. The measurement of the basal metabolism, ie, the energy used by all the tissues at rest, related to the body surface area, gives similar results.

Parallel with this constant reduction in the

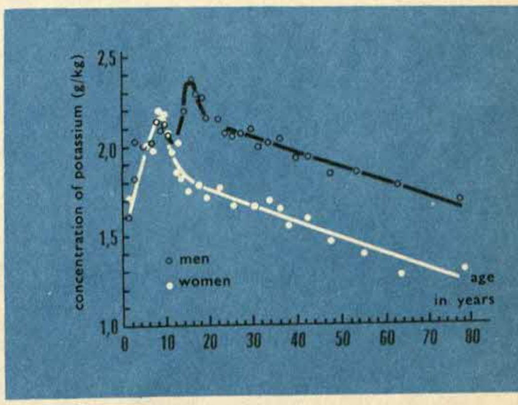


*Fig. 1. The fall with age of the concentration of potassium in the human organism.*

(1) Ageing: *the point of view of the practising doctor and that of the physiologist are different. The doctor thinks first of illness, rather than of the effects of age, when he sees a twenty-year-old patient. He associates ageing effects only with old people. The physiologist, on the other hand, considers that ageing begins immediately after birth.*

(2) Active mass: *the mass of tissues responsible for the energy exchanges of the organism.*

(3) Collagen fibre: *one of the two types of fibres found in connective tissue. It is responsible for the phenomenon of sclerosis or hardening.*

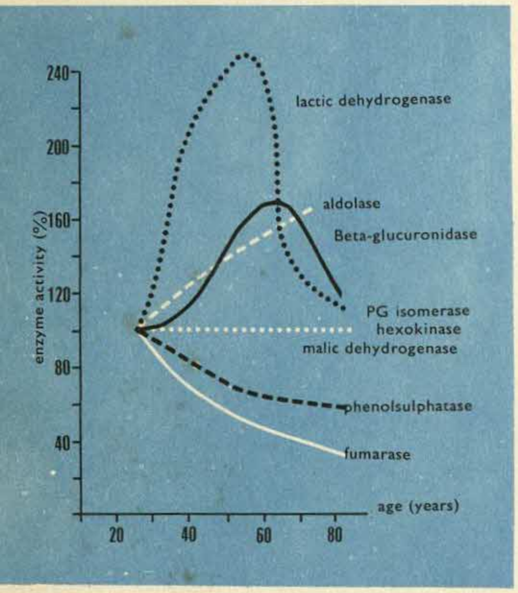


*Fig. 2. Variation with age of the activity of certain enzymes in the same organ (human aorta).*

mass of the tissues responsible for our energy exchanges and our various metabolic activities, there is a movement in a contrary direction of the 'inert components' of the tissues, which increase in quantity with age. For example, the total fat in the human body rises from 16·5 per cent of the body weight between twenty-two and twenty-nine years, to 22·6 per cent between forty-eight to fifty-seven. And it is not only a question of those fat deposits which tend to 'thicken' our silhouettes; a certain degree of fatty degeneration is also found in the interior of many organs. The interstitial tissue, particularly the collagen fibres,[3] increases regularly as the years go by and the macromolecules of collagen also seem to change in structure as they age. Their thermal contractility increases, whereas their solubility in acetic acid and their susceptibility to the action of a special enzyme, collagenase, decreases. The ground substance, itself, a sort of cement which fills in the spaces between cells, also changes with age.

In connection with this diminution in the mass of the active tissue in the organs of the individual, it is of interest to see whether the various tissues remain physiologically constant during the period from the end of growth up to an advanced age. Technically speaking, it is not easy to answer this question. If the respiration of a piece of tissue is studied *in vitro* the consumption of oxygen per unit of wet (or dry) weight is frequently found to fall with age. This observation, however, could just as well be interpreted as indicating a fall in the number of functional 'cellular units' (which is in fact the case in the great majority of organs, as has just been shown) as indicating a diminution of the respiratory exchange in the surviving cells. For this reason, it is now usual to relate the content of the substances that are being measured to a basic unit of deoxyribonucleic acid content. But even if these precautions are taken, it is impossible to show a simple chemical change common to all types of tissue. At most, it is possible to show that the cells which renew themselves continuously in the adult generally remain biochemically constant throughout life, while the permanent cells, neurones, for example, have a tendency to become loaded with fats and pigments, which can be interpreted as metabolic waste products.

The study of variations with age in the intracellular enzymes has been very searching in the past few years, but in this case too there seems to be no general rule. In striated muscle, for example, one finds no change with age in the enzymes concerned with glycogen breakdown, or in aldolase; hexokinase, on the other hand, diminishes considerably. In the human aorta (fig. 2) hexokinase, phospho-gluco isomerase and malic dehydrogenase remain at a constant rate of activity from twenty to eighty years of age, but fumarase and phenolsulphatase diminish regularly, aldolase increases, and lactic dehydrogenase and β-glucuronidase appear to have a peak of activity between fifty and sixty-five years. There seems to be little doubt, therefore, that the various enzyme-systems in a tissue change differently with age. Moreover, in the same individual, the same enzyme may diminish in one tissue and increase in another.

## *Physiological changes*

What are the consequences to the organism as a whole of the changes just described? The effects find their expression essentially as a progressive diminution in the functioning of different organs; in other words, a reduction of their functions and capacities. Without going into details, here are some important examples from the species which has been best studied—our own.

Fig. 3 shows the variations with age, from twenty-five to eighty-five for men, in the maximum volume of air that one can expire after taking a deep breath. It will be seen that in this sample of healthy subjects the ventilatory 'constant' changes from about five litres at twenty-five to a little more than three litres at eighty-five. Between these two ages the decline is regular and almost linear. In women, the change is in the same direction although the absolute values at the different ages are different.

A reduction of this type is found equally in a very large number of functions. The cardiac output diminishes regularly from the twentieth year, as does the systolic volume and the rate of heart-beat. So does the volume of gastric juice secreted after a standard test meal, in its content of hydrochloric acid and of pepsin, the principal enzyme for the digestion of proteins in the stomach. In the kidney there is a regular fall in the amount of glomerular filtration, in tubular excretion and in the maximum capacity of the tubules to excrete and reabsorb. The maximum power that can be exerted by any muscle is reached between twenty and thirty years, followed by a continuous diminution which is accelerated with age. The systolic blood pressure, on the other hand, like the peripheral vascular resistance and the circulation time, increases regularly from twenty to an advanced age. That these last phenomena are not solely due to increase in the incidence of atheroma[4] is shown by the fact that similar changes are found in the rat, a species in which this degenerative disease is not found under normal conditions.

The endocrine glands, for the most part, follow a similar course. The lowering with age of the level of fixation of radioactive iodine by the thyroid begins at twenty years of age and continues linearly. In both sexes, excretion in the urine of androgens (male hormones) diminishes more between puberty and the forties than it does after this age. It should be noted that this diminution is parallel with the diminution in libido, in spite of the 'corticalization' of sexual behaviour in human beings.[5] The oestrogens (female hormones) begin to diminish in women well before the menopause. Here again there is a parallel between the falling hormone levels and the diminution of fertility with age, a phenomenon which is more easily studied in other mammals or in birds than in human beings. In all cases which have been studied it has been found that the number of young produced by the female each year reaches its maximum shortly after sexual maturity and that thenceforward it decreases regularly. The adrenal cortical hormones, which play such an important part in the adaptation of our organism to the continuous adverse pressure of environmental factors, diminish very little with age. The secretion of the different hormones from the anterior lobe of the pituitary, which can be determined directly or indirectly, seems to vary little with the years, both thyrotrophic hormone and growth hormone, for example, being produced in comparable quantities. In women, the gonadotrophic hormones are produced in greater quantities after the menopause, and in men, between the ages of forty and sixty-five, as if in response to the diminution in activity of the ovary and the testis respectively.

The nervous system likewise ages from a very early period. The studies that have been made of it have been mainly of the sensory receptors. The eye is one of the organs which suffers earliest from the effects of time. The amplitude of the response of the lens to accommodation diminishes from the age of ten and is practically nil by the sixties. Adaptation to low intensities of illumination declines regularly from the age of twenty, as does the time taken to recover from the effects of dazzling, and the critical frequency at which a series of intermittent luminous stimuli appear as uniform illumination.

The ear ages as early and as rapidly as the eye. From forty years of age there is a noticeable diminution in the ability to hear high-pitched sounds. The receptor organs for touch and taste follow a similar course. At the same time, one notices a progressive slowing of the maximum speed of conduction in the motor nerves. In the brain itself the consumption of oxygen and the cerebral blood-flow diminish from infancy, parallel with the density of the cortical neurones (fig. 4). The electroencephalogram shows evidence of a diminution in the frequency of the basic rhythm; at the same time, the reaction of visual arrest becomes worse and the hyperpnoea[6] test is more and more sensitive.

All these facts explain very clearly the increase in the reaction time to a given auditory or visual stimulus, a psychomotor test which has become one of the most useful there is for measuring the rate of ageing in individuals.

## *Diminution of the faculties of adaptation*

The slow and progressive falling-off indicated by these examples leads little by little to a diminution of the physiological possibilities of the organism and to a narrowing of the safety margin of our various functions. The consequence is a progressive loss of the adaptability which the individual shows to the changes continually taking place in his environment. For a long time this process remains hidden, for the safety margin is considerable to begin with, and it is not often in the ordinary run of life that we have to exert its possibilities to the maximum. But after the age of fifty, things are no longer the same, the organism begins to tire more easily and to adapt itself less and less successfully.

Nevertheless, the constancy of the internal environment is maintained at all costs, as long as some serious illness does not occur to complicate the picture. In the healthy old person the blood volume and the number and structure of the red blood-corpuscles remain the same as at twenty years. In spite of the atrophy of the organs responsible for haematopoiesis, smears of the bone marrow, the lymph nodes and the spleen preserve the same aspect. The level of sugar and the acid-base balance in the blood remain at their usual levels. At most, one may find some diminution in the total blood proteins, perhaps due partly to nutritional difficulties. But this constancy of the

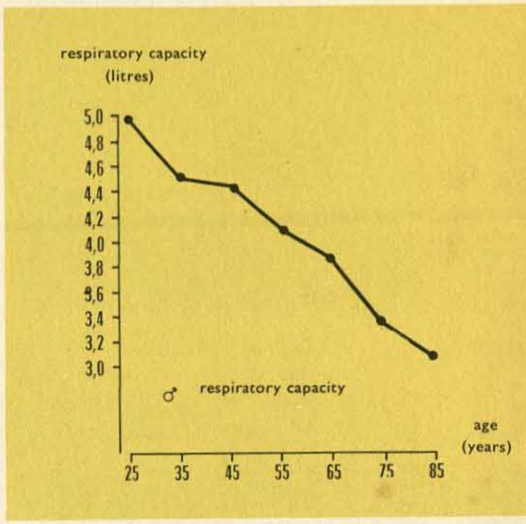


*Fig. 3. Variation with age of respiratory capacity in men.*

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(4) Atheroma: *a degenerative condition of the cardio-vascular system of higher vertebrates. It consists of lesions of the lining of the arteries, leading to the deposit of fat and later of calcium salts which cause a hardening of the walls and a reduction of the calibre.*

(5) Corticalization of sexual behaviour: *this expression relates to the greater effect of psychological phenomena on the simple endocrine factors in the sexual behaviour of higher mammals.*

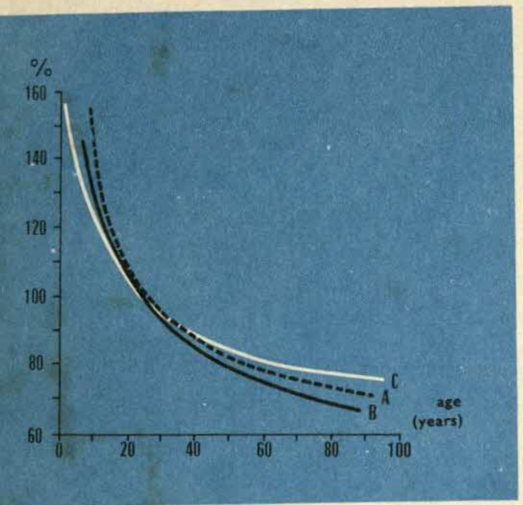


*Fig. 4. The fall with increasing age of (A) the cerebral blood-flow, (B) the consumption of oxygen by the brain, and (C) the density of cortical neurones in man. (After Kety, 1956).*

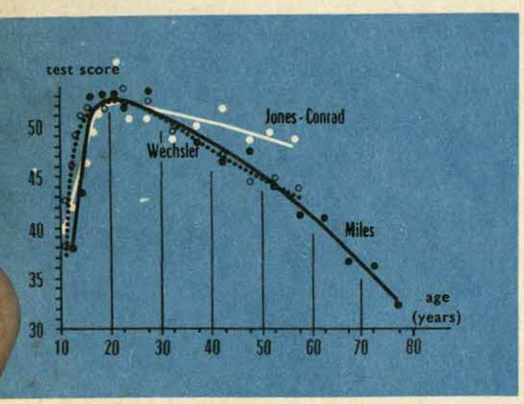


*Fig. 5. The influence of age on general intelligence, as estimated by the scores in tests devised by Wechsler, Jones-Conrad, and Miles.*

internal environment is maintained with increasing difficulty, and any slight illness which would be shrugged off by a young person with practically no change will cause more important and more prolonged effects in an old person. The injection of a certain quantity of glucose into the blood stream leads to a higher and longer-lasting hyperglycaemia in those over sixty than in younger persons. Likewise, as the years go by resistance to heat and cold diminish, adaptation to effort becomes less and less efficient, the kidney responds less well to the same dose of pitressin, etc. Slowly, progressively, but inexorably the involution of the ageing process transforms the young adult into an old person.

## *Psychological consequences*

The ageing of our intellectual capacities follows in general the same pattern as that of our physiological functions. In fact, the early onset of some kinds of intellectual decline was demonstrated by the psychologists well before biologists became interested in the problems of ageing. But the aptitudes which are measured by different psychological tests are only a part of our psychic life. 'Experience', which is so important in everyday life, cannot really be measured by any technique, yet obviously experience increases with age and must play a more and more significant part in our actions.

There is no doubt that different types of memory are affected early by the ageing process, at least in those of average or low intellectual level. Memory for the immediate past seems to be affected least. Memory for concrete facts starts to diminish after the age of thirty, but that for logical conclusions and especially for forming associations is already diminishing from twenty onwards. The capacity for learning, which calls not only for memory but also for understanding given problems, diminishes very early, as do enthusiasm and reasoning power, and fatigability rises.

All this explains why various studies of overall mental efficiency, in which batteries of tests are used and which cover many intellectual functions and are therefore thought to measure the intelligence of the individual, give evidence of a regular decline from about the twentieth year onwards (fig. 5). It is possible to object that these studies have mostly been carried out on the less favoured sections of the community and so may not apply to the more intellectual ranks of modern society. But then, how are we to interpret the findings of H.-C. Lehman on the age of 'best performance' in many eminent people in walks of life as different as chemistry, music, physics and novel writing? Lehman took the opinion of fellow specialists on the age at which the most important work of several hundred well-known people had been done. Shown graphically (fig. 6) it will be seen that the frequency of publication or production of major works increases rapidly from fifteen or twenty years to reach a maximum between thirty and forty, after which it decreases regularly. The agreement between the various widely different fields of intellectual endeavour is striking. Generally, the top of the curve is between thirty and thirty-nine years. It can be earlier, even twenty to twenty-five for certain poets, or later, forty to forty-five for architects and novelists, but such deviations are fairly uncommon. Thus we see that even if Lehman does show the period of maximum intellectual efficiency as rather later in the *élite* of the population than in the rest, this efficiency nevertheless still occurs relatively early in life.

## *Differential ageing*

The facts presented in the last few pages lead one to conclude that in man and the higher animals ageing is an inexorable process which continues slowly and silently throughout life. But the researches which have enabled us to reach this conclusion have also revealed another important point. If ageing is unavoidable, its speed of progress may nevertheless vary. Not all the members of a given species age at the same rate: some will be in advance of, and some behind, the average. Why is this?

In certain cases differential ageing is due to genetic factors. It has been known for years that the average life-span in some human families is longer than in others. Years ago, Raymond Pearl demonstrated this statistically by comparing the total ages of the six immediate ancestors (parents and grandparents) of two groups of people: on the one hand, nonagenarians and centenarians in good health, and on the other, individuals taken at random. The sum of the life-spans was significantly greater, by sixty years, or 16 per cent, in the case of the ancestors of those still alive at ninety or over. Pearl also showed that if one compared the life-span of children and their parents, the older the father was when he died, the longer was the life of the child. Other researches carried out on *uniovular* and *binovular* twins have also shown the importance of heredity in the progress of ageing. In identical twins the speeds of ageing are generally remarkably similar and the simultaneous occurrence of certain physiological or psychological 'accidents' is very striking. This is not only the case in man; the various strains of the fruit fly, *Drosophila*, for example, have life-spans that are often different.

One particular case of differential ageing, probably of genetic origin, is the difference in longevity between males and females of the same species. In man and the mammals the potential and average duration of life in the male is below that of the female, although the latter begins to age earlier (fig. 1).

However, the life-span of an individual does not depend on a single gene. At most, heredity only determines the potentiality for longevity and in fact ecological factors play a great part in determining how long a person will live. Among the factors of the environment, two in particular are well recognized: diet, and the use or lack of use of various functions. The importance of the first was discovered by the American nutritionist, MacCay, in the course of his famous researches which opened the way to modern knowledge of this subject. These showed that in the rat there is a correlation between, on the one hand, the abundance of food provided and the rate of growth, and, on the other, the length of the life-span and the occurrence of certain degenerative illnesses. He compared two groups of animals from the same stock which were kept under similar conditions throughout their lives. The control rats were fed *ad libitum*, ie, given as much as they could eat, and the experimental animals were given a reduced diet which was balanced in quality but restricted in quantity, so that their growth rate was reduced. In the normal control rats skeletal growth ceased after about 175 days, and all of them were dead within two and a half years. But the retarded rats, restricted in calories, went on growing slowly for 300, 500, 700 or even 1,000 days, according to the period at which they were put back on to a normal diet. The important fact here is that this restraint of growth by means of restricting the diet was always accompanied by a considerable increase in the life-span. During the first experiment, one of the restricted animals lived to the record age of 1,421 days, which was nearly double the average life-span of the control rats. In the second experiment, all the normal rats were already dead when some which had been restricted for 1,000 days began to grow again on a fuller diet. Another important observation was that the lengthening of the life-span was accompanied by a slowing-down of the appearance of age-changes in the collagen fibres of the connective tissues, and particularly, it seems, by a much smaller incidence and a later occurrence, of the degenerative type of illness, and also of the incidence of lymphosarcoma of the lungs and of renal sclerosis. The experiments have since been repeated by numerous other research workers using various species of rodents, and all have obtained the same favourable results.

Naturally, such results cannot be applied directly to human ageing. For one thing, growth is more variable in rodents than in primates, because the epiphyseal cartilages of the former do not fuse soon after sexual maturity, as they do in the latter. But of the part played by nutritional factors in the premature ageing of some functions in man there can be no doubt. It has been shown, for example, that there is a definite correlation between the percentage of fats of animal origin in the daily diet, the level of cholesterol and β-lipoprotein in the blood[7] and the frequency of atherosclerosis. Though suboptimal nutrition and certain dietary deficiencies are mainly responsible for the low average life-span in under-developed countries, in our own it is undoubtedly excessive eating and lack of dietary balance, combined with too little exercise and the increasing pace of our day-to-day existence, which are leading to premature ageing of certain of our functions.

Another way in which the environment may influence the rate of ageing is if it acts through agencies which stimulate or reduce the use we make of certain functions. Muscular power gives a clear example of this. We indicated earlier that the average maximum efficiency of any particular muscle group is found early in life, at about twenty years, and that after this there is a gradual reduction in muscle power. It is only necessary, however, to examine a group of persons from different professions to see that within each age group there are considerable variations round this mean, variations which are clearly correlated with the types of life led by the various individuals. The sedentary worker and the office worker who take no exercise lose their muscular strength much more quickly than do the peasant and the manual worker, or even the intellectual worker who participates regularly in some sort of sport.

On the other hand, tests of vocabulary give a maximum score at a later age and show a slower decline in those who follow intellectual professions and who must rely all the time on their powers of memory, than in manual

(6) Hyperonoea: *acceleration of breathing movements.*

(7) β-lipoproteins of the blood: *a fraction of the lipoproteins of the blood plasma which seems to rise concomitantly with the progress of atheroma.*

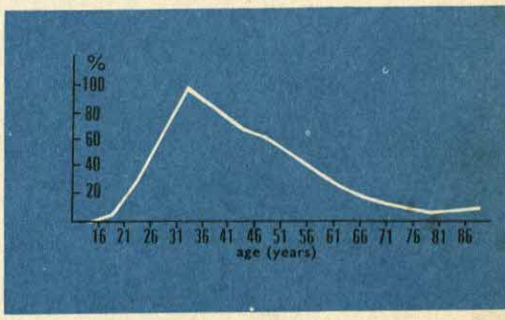


*Fig. 6. The influence of age on scientific and technical productivity. The chief discoveries of 933 distinguished scientists.*

workers, who do not need to keep alert in the same way. In other words, it appears that the muscles, lungs and brain all age more slowly if they are kept fully employed over a longer period.

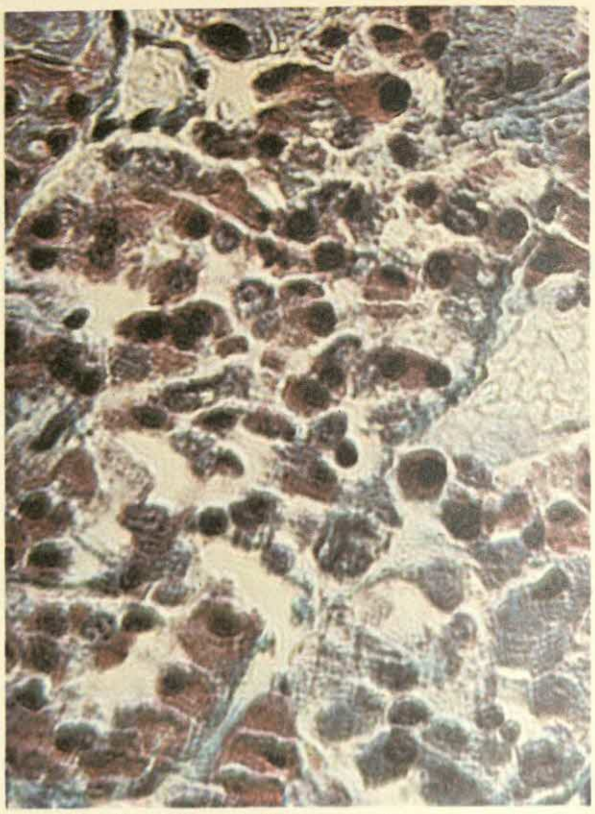
## *Therapeutic possibilities*

At present, there seem to be two possibilities for treatment: one is to slow down as far as possible the rate of ageing itself; the other is to correct some of the anomalies found in age, which are, in fact, reversible.

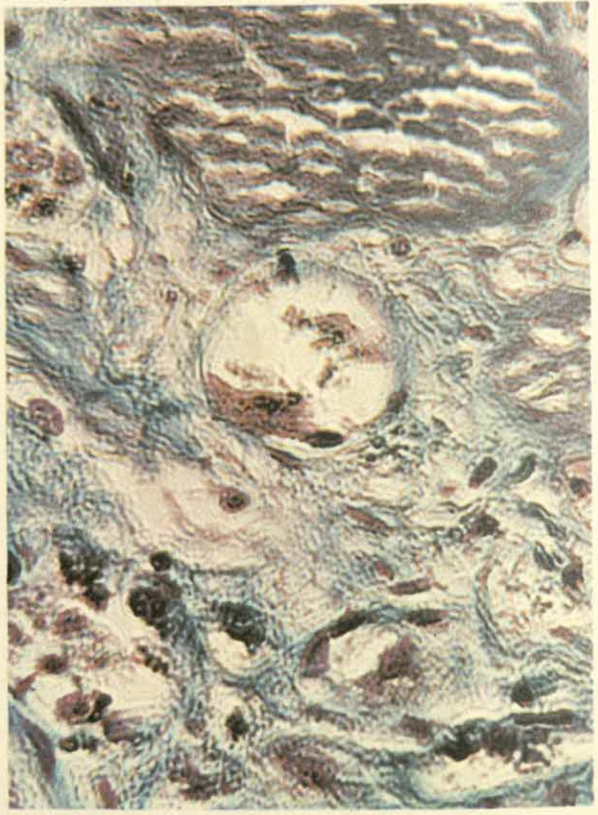
The prophylaxis of the accelerated ageing of certain functions which is due to bad physiological conditions of life imposed by the extreme specialization of our industrial society, is founded principally on the idea of differential ageing. There is no doubt that a poorly adjusted dietary regime, and also a prolonged lack of balance between our physical and intellectual abilities, gravely affect the future of many adults and cause them to age more quickly than they should. Similarly, a poor adaptation of our conditions of work to our psychological and biological possibilities leads to the same result. It is rightly one of the chief objects of modern gerontological research to try to lay down clear rules for the hygiene of those of mature age.

The correction of the reversible disorders of age is at present unfortunately limited to the correction of a few particularly unfortunate effects. Thus the stimulation of protein anabolism by means of steroid hormones—either natural, such as testosterone, or synthetic, such as androstanolone base—and a careful dietary regime allows us to correct over long periods the extreme fatigability of old people, to improve their locomotor system and maintain them much longer in a satisfactory physical and mental state. It seems that failing memory, so conspicuous in old people, can be temporarily helped by the use of certain drugs. The perfecting in recent years of techniques of re-education and re-habilitation of hemiplegics has transformed the prognosis for sufferers from many cerebral vascular accidents—those who even a few years ago would have been considered beyond help—which shows that the organism continually retains certain possibilities of readaptation.

True rejuvenation, in which some miracle medicine would take us back through time and efface the traces of the years, exists unfortunately only in the realms of science-fiction. None of the shock treatments which have been publicized so much in recent years have shown, experimentally, the slightest signs of success.



*To the child and the average person, age is represented by the lined face which we see in the picture opposite. But ageing is actually something quite different. It is, in fact, a very slow process which begins even in adolescence. One after another, at different rates, the organs of the body atrophy. Shown on this page are two stages in the evolution of the pituitary gland. Above, a section of the gland in a man of middle age, and below, that of an old person. (Mag. × 700. Photos Lod).*



# Fatigue

### *Pierre BUGARD*

*Physiology teaches us that the excitable tissues of the organism are capable of functioning at different 'loads'. An economical load, which might be called the 'cruising load', can be maintained for a long time, whereas a more exacting 'peak load' involves greater effort. In fact, the cruising load has several levels of activity, the highest of which is the 'critical load'. Fatigue comes on much more rapidly once activity passes the critical load and approaches the peak load.*

Fatigue can be considered in two ways:

(a) The observer will notice that all organic activity which is determined by a constant stimulus leads to one of two possibilities: either the activity can be continued for a very long time (for example, the beating of the heart at the normal rate of about sixty beats a minute), or it can no longer be sustained, in spite of the stimulus being increased. By the physiologist and the biochemist fatigue is considered from the point of view of the mechanisms that determine this decrease in activity; in other words, the bottlenecks which appear in the circuit, the way in which the decrease is expressed, and the processes which tend to compensate for diminished activity.

(b) Fatigue is also a feeling experienced by the individual. This subjective psychological sensation is comparable to others, such as thirst or pain. But it is also the feeling of a man regarded as a psycho-physical whole, placed in a certain situation in an environment from which he cannot be separated. From this point of view, of a man struggling with himself and his surroundings, fatigue becomes a mode of behaviour. It is, in fact, a refusal to be involved.

## *Muscular fatigue*

Although in the modern world muscular effort has become subordinate to psychological effort, it is worth analyzing muscular fatigue for several reasons.

1. It is possible to assess physical labour and muscular fatigue because measurable quantities exist, ie, forces or powers, as well as relatively simple electrophysiological data.

2. Taking an overall psychosomatic view, fatigue is apparently a reflection of central nervous phenomena on to the muscles. The excitability of muscle is controlled by basilar nervous centres through neurotrophic pathways (this is the old concept of the chronaxie of subordination put forward by Lapicque), but it is also dependent on the general endocrine and metabolic state through humoral pathways. Thus, nervous fatigue leads to diminished muscular capacity and this change is assessable by peripheral measurement.

3. One cannot dissociate muscular fatigue from the work which has caused it. We distinguish between *local* effort which involves less than one-third of the total muscles (that is, less than 10 kg out of a total of some 30 kg); *regional* effort which uses between one-third and two-thirds of the mass of muscle; and *general* effort which brings more than two-thirds into use.

Fatigue is shown in a different way when it is the result of *static* work, in which there is no movement, as compared with *dynamic* work in which there is a succession of contractions and elongations of the muscle.

## *Ergodynamography*

This is an old method that has recently been re-adopted with the aid of apparatus in which the power is maintained at a constant level; it enables us to define the fundamental

(1) *If the work being done is equal to or less than the reconstitution factor, then the work can be carried on for a long time, but once it exceeds this factor, exhaustion will follow as soon as the reserve of energy (which is small) has been exhausted. This relationship accounts for the capacity for local, regional, or even general effort and can be applied to the scientific study of athletic events. It also includes the concept of a 'second wind', as applied not only to the whole organism but also to its separate parts.*

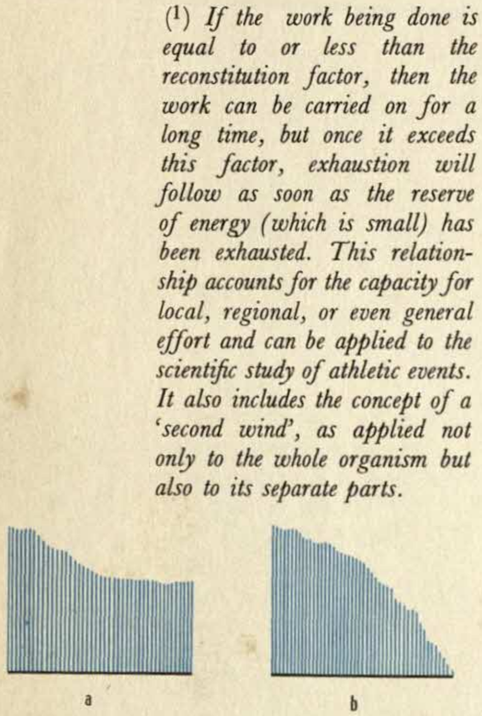


*Fig. 1. Ergographic curves: (a) work carried on without fatigue; (b) progressive fatigue.*

(2) *The basic electromyogram of a fatigued muscle shows a tendency towards synchronism of the potentials of several motor units with a frequency of about 9 per second, which is close to that of the trembling which accompanies fatigue.*

(3) *The variations in excitability demonstrated by this technique depend not only on local changes in the fibres, but also on the phenomena of subordination to the nerve centres or even on more general hormonal and metabolic causes, as we have found in certain pathological states of insufficiency or hyperactivity of the adrenal cortex.*

aspects of muscular fatigue. The critical power in the case of dynamic effort is based on the existence of a simple relationship between the time during which the effort will inevitably be interrupted by muscular exhaustion and the work actually accomplished. This depends on two factors: the energy reserve and the reconstitution of the energy potential of the muscular contraction.[1]

In static work a decline in the amount of blood circulating in the muscle appears as soon as the force of the contraction reaches about one-sixth of the maximum; in this type of work the peak load is rapidly reached.

## *The electrophysiology of fatigue*

Electromyography records the electrical activity of muscle while it is contracting. This activity comprises small, irregular variations of potential during weak contractions and larger rhythmic variations during stronger contractions. Muscular effort during the critical load leads to fatigue, resulting in variations which have been interpreted differently by different researchers, but all of them are expressed by an increased amplitude of the electrical phenomena. The return of the integrated electromyogram to normal after intense local effort takes more than an hour. Besides this, in regional or general effort at a critical load there appears a diffusion of action potentials to those muscles that are not directly involved in the effort. These are the muscles used to fix the joints, but the reaction does not spread to the antagonistic muscles.[2]

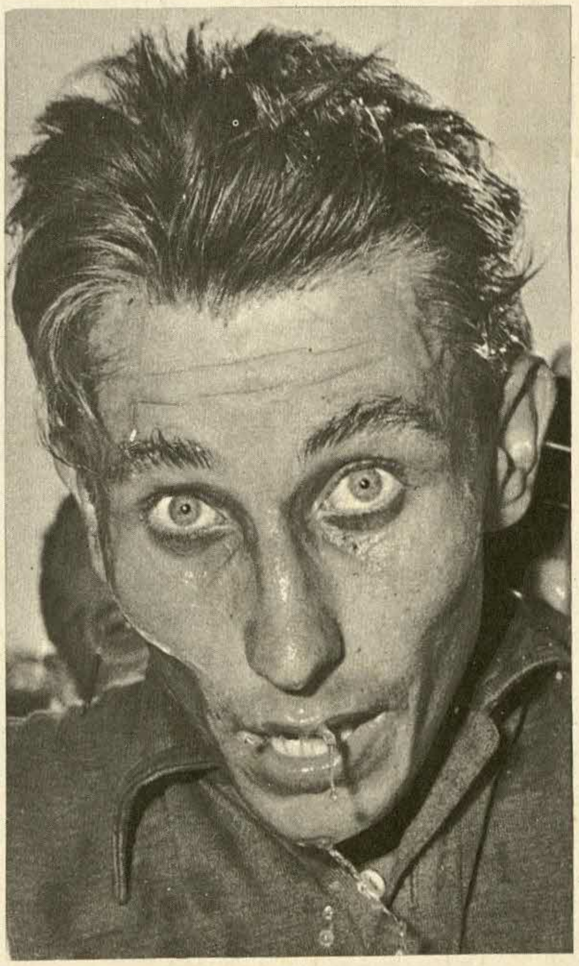
(a) If the motor nerve of a fatigued muscle is electrically stimulated, there is a considerable fall in the strength of the mechanical contraction compared with normal; this is in contrast with the persistence of the action potentials in the muscle.

(b) The measurement of the intensity-duration curve for the threshold of motor response to an electrical stimulus applied to the nerve or muscle through the skin gives some interesting practical information, not only in the case of the exhausted athlete who has just performed a tiring exercise, but also in that of the fighter, the airman, or the worker whose fatigue is not the result of purely muscular effort.[3]

## *Circulatory and respiratory adaptations in fatigue*

Muscular effort causes an increase in the blood flow in the muscles which may amount to 160 cc per minute for each 100 g of muscle during intense effort. If more than one-third of the mass of muscle is involved therefore, the heart will be unable to maintain a sufficient output. So it is clear that the more of the mass that is involved, the more will the general cardiac and respiratory phenomena be limiting factors. Changes in the heart-beat and output, the arterial pressure and the consumption of oxygen during effort and fatigue have led to practical results in the rational conception of methods and working conditions (Lehman, Brouha).

A speeding-up of the heart-beat may precede the start of an effort, which shows how important is the part played by psychological factors even in the most ordinary muscular effort. The consumption of oxygen during dynamic work has enabled us to establish the idea of muscle efficiency, which can be more than 25 per cent, provided that the amplitude of the contraction, and its force, speed and frequency are such that the muscle is working under optimum conditions. However, it falls



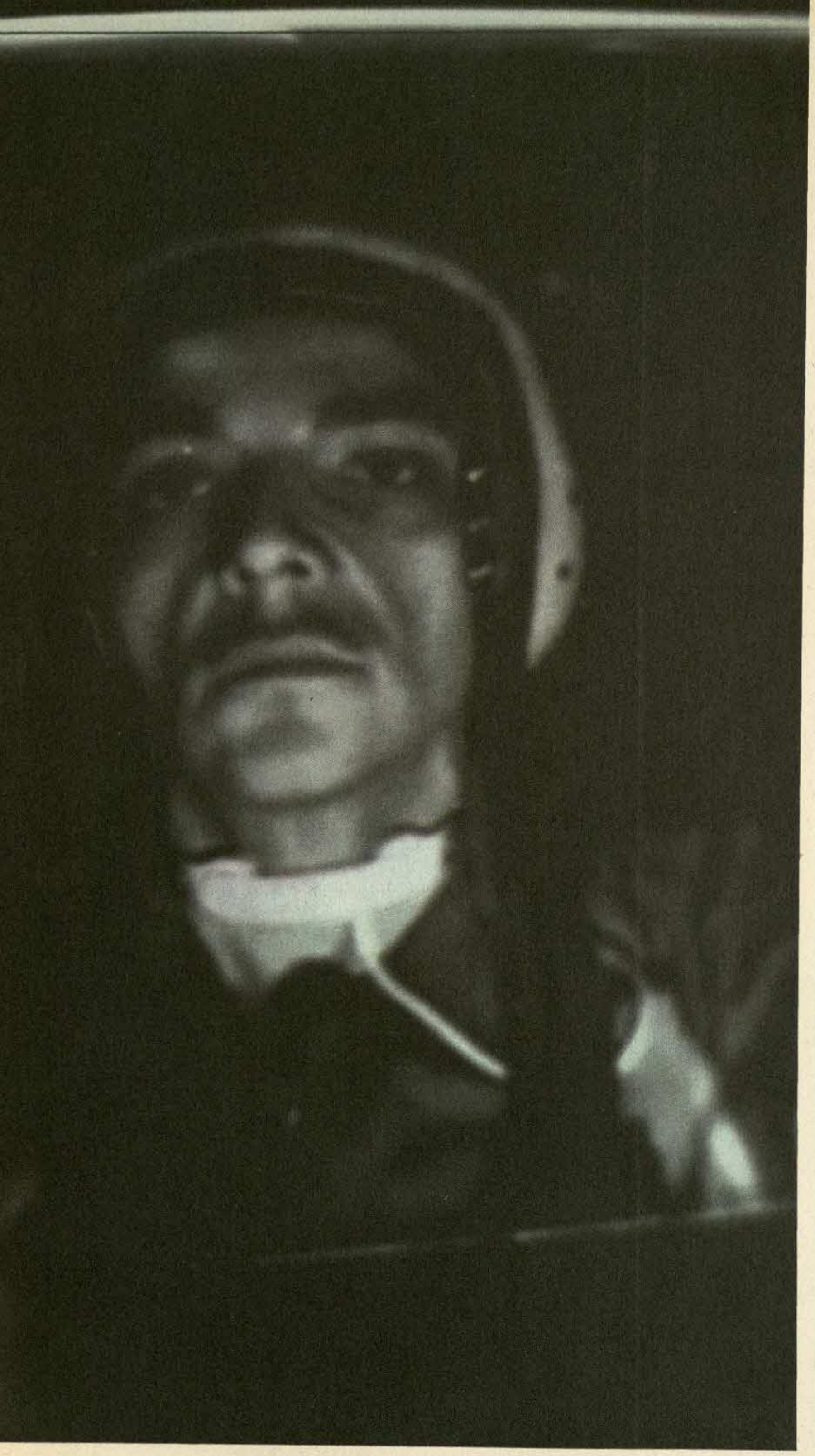
*A characteristic example of fatigue brought about by dynamic work. The effort put out by a racing cyclist gives us a striking example of an experiment carried out* in situ. *(Jacques Anquetil during the Tour de France, 1959. Photo Presse Sports).*

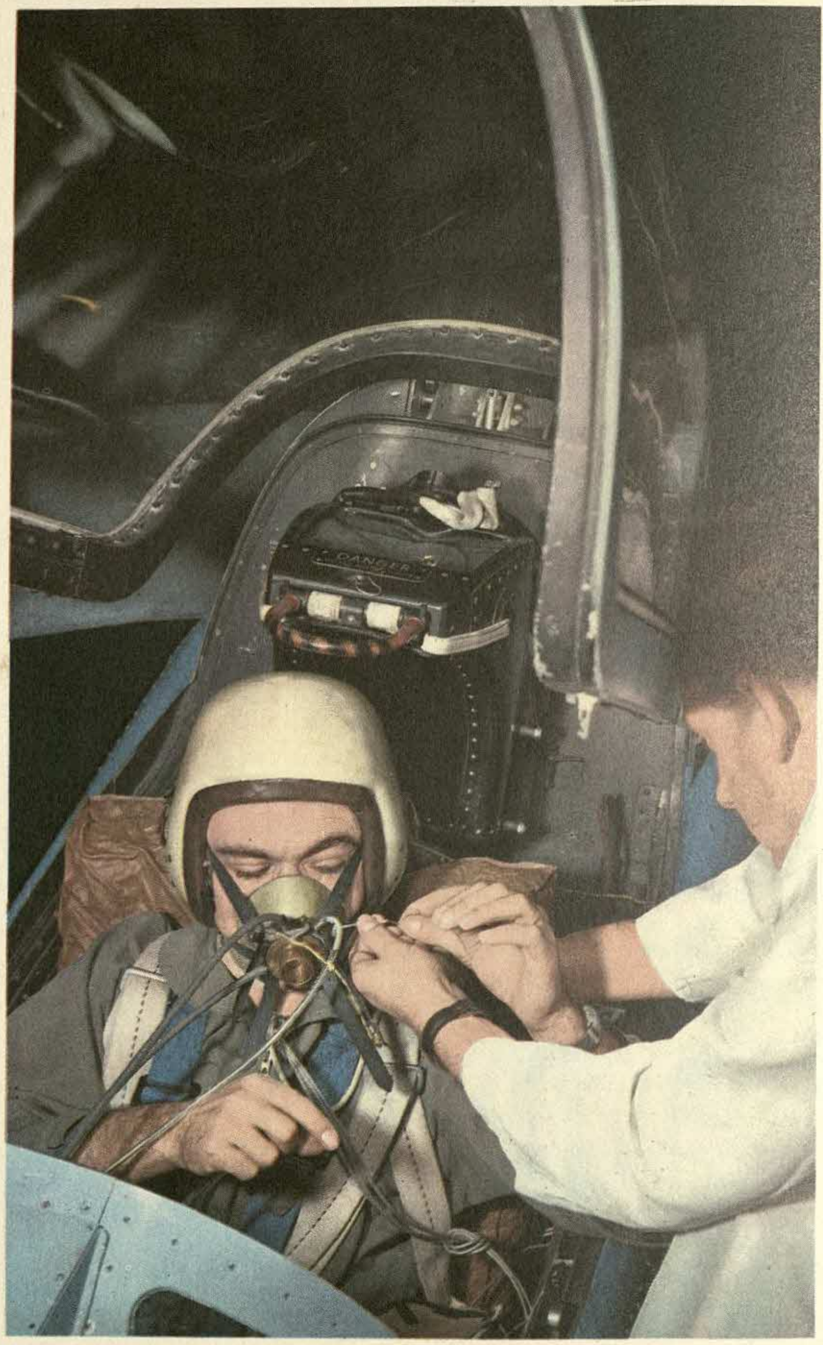
(4) *Fatigue of the central motor centres is not evenly distributed, since tone, which is associated with the white fibres, and voluntary activity, which depends on the red fibres, are not controlled by the same motor neurones. The motor neurones of the anterior horn of the spinal cord are under the influence of activating impulses (from the mesencephalon) and also of inhibitory ones. The lowering of the frequency of impulses from the motor neurones of the cord may be due to local fatigue and also to central inhibition. In short, the margin of safety when working at a constant load, ie, resistance to muscular fatigue, is greater for the peripheral motor systems than for the nervous centres, which are the most vulnerable.*

(5) *This form of fatigue more often affects persons who have a defect of refraction, but it also affects those with an exophoria (a divergence of the axes of the eyes when at rest), or an esophoria (the reverse tendency, with excessive convergence). In these last two conditions the antagonistic muscles have to make an abnormal effort when extra visual clarity is called for, or when the light is poor, and this quickly results in fatigue.*

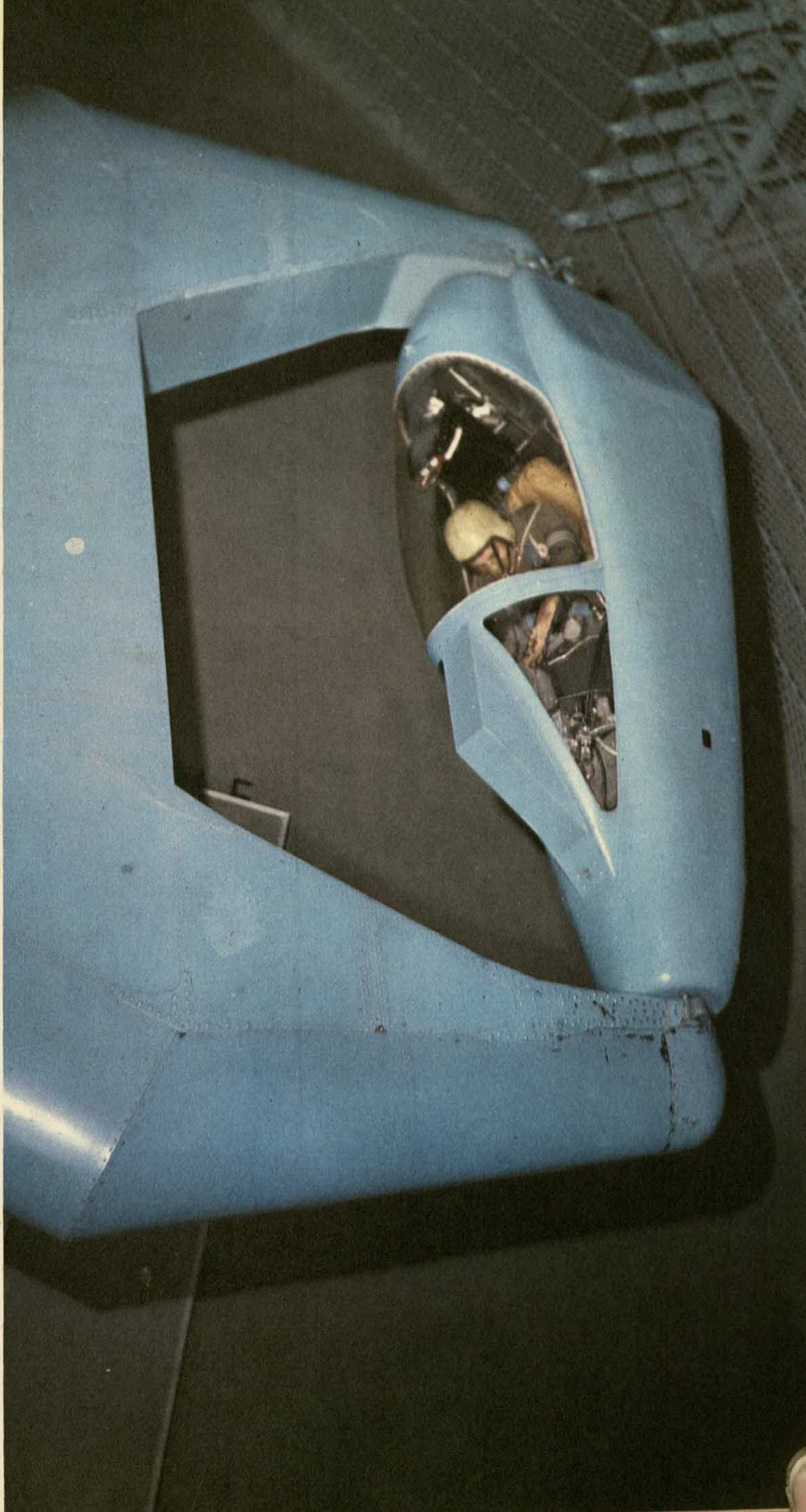
(6) *The more serious this fatigue, the more it tends also to affect neighbouring frequencies, and it may extend to the other ear if the first stimulus was unilateral. Real acoustic damage is more than fatigue and constitutes a permanent lesion. In noisy occupations it may be difficult to draw the line between fatigue and permanent damage.*

# The effects of acceleration





*Provided the human machine is given the chance of adaptation through suitable exercises, it can put up with conditions that are very different from those we usually find on the surface of the earth. This applies especially to very high degrees of acceleration, such as are experienced by astronauts. At the flight test centre at Brétigny-sur-Orge in France we see preparations for an experiment in which the resistance of the organism to such conditions will be measured. In the centre, in the cockpit of a human centrifuge, preparations are being made for measuring the changes in the pulmonary mechanics. These measurements also make it possible to estimate the value of the usual protective measures (anti-gravity suits). The cockpit is the same as that of an aeroplane, with all its controls. Right: the pilot is submitted to an acceleration of 4 g for one minute in the centrifuge. During this period, all the parameters of the respiratory and circulatory systems are measured in order to estimate the changes exerted by forces of inertia. Left: during the test, the pilot is kept under constant observation by a television camera inside the cockpit. The doctor can watch his behaviour on a television screen in the control post. (Photos Lod).*



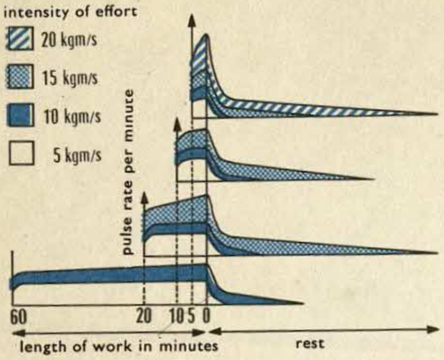


*Fig. 2. Variations in the pulse rate brought on by efforts of different intensity. (After E. A. Müller and K. Karrasch).*

(7) *Chauchard believes nervous fatigue to be a general reaction following adverse conditions resulting from multiple stimulations from the exterior and the interior. The mid-brain centres and the reticular formation of the medulla play an important part in regulating the nerve input and its diffusion towards the cortex and the autonomic centres. Physiological fatigue leads towards sleep, because the reticular formation temporarily loses its power of ensuring vigilance and cerebral activity. Pathological nervous fatigue is bound up with a disequilibrium which acts as a stimulus to this regulatory mechanism, and disturbs vigilance and the autonomic centres. These manifestations will be similar whether the disturbance originates from the exterior or from the organism itself, and whether it is started by humoral or emotional factors.*

(8) *As an example, there may be in the first instance an increase in the cellular elements of the blood, originally due to the stimulation of the blood-forming centres, and to the contraction of the spleen. This may, however, be masked later by a dilution of the blood caused by (a) secretion of pituitary hormones (particularly antidiuretic hormone) which reduce loss of water, and (b) the appearance of aldosterone in larger quantities from the adrenal cortex, to counter perspiration losses.*

considerably once fatigue appears (slow dynamic work, movements of feeble amplitude—and at the limit, static work—work carried out by small muscles which are overloaded).

Regional or general muscular effort at peak load causes the appearance of a 'debt' in the organism, not only of oxygen, but also of metabolic substrates. This debt, ie, excess of output over intake, is one of the characteristics of fatigue; it has to be repaid during rest and if there is no rest, the fatigue becomes pathological.

It has been worth while to sum up the mechanisms of muscular fatigue because they throw light on the problem of fatigue in other systems and the general problem which concerns us here.

## *Fatigue in the command system*

In work at the critical load, the frequency of nerve impulses (about 6 per second) causes no fatigue in the nerve fibre, or in the motor end-plate, or in the cell-membrane of the muscle fibre. Muscular tone, which can be maintained for very long periods, involves impulses with a frequency of 3 to 5 per second. The critical frequency, for effort at a constant load, is about 15 per second.[4]

## *Fatigue in the supply system*

For effort at critical power, the supply of oxygen required is about 23 cc per minute for each 100 g of muscle. This supply will be endangered once the mass of muscle involved exceeds the possibilities of the cardio-respiratory system. This will happen even in normal atmospheric conditions, and obviously in a rarified or excessively hot atmosphere the supplementary effort from the ventilation and the circulation will limit still further the amount of oxygen available and lead to fatigue beginning earlier. When working at a critical load, the speed of diffusion of oxygen and metabolites through the membrane of the muscular fibre is also a 'bottleneck', and so forms a contributory factor in fatigue.

The contractile proteins of the fibre (actin and myosin) and the provision of the energy necessary for their contraction by the high-energy phosphate compounds (mainly adenosine triphosphate, ATP) are also disturbed by fatigue. The resynthesis of these compounds depends on energy obtained through anaerobic glycolysis, and partly from the aerobic breakdown of sugars. Fatty acids and the portions of amino acids remaining after de-amination may also contribute to the supply of energy. There is, therefore, side by side with the general biochemical syndrome of fatigue which we shall discuss later, a local biochemical aspect of great importance. ATP and similar compounds can provide energy for only very short periods, but their resynthesis is very rapid, while the resynthesis of glucose from lactic acid under aerobic conditions is much slower.

## *Sensory fatigue*

*Visual fatigue* is shown by ocular symptoms (abnormal sensations, discomfort in the eyes, blinking, and pain) or by symptoms affecting vision itself (blurred vision, the appearance of coloured fringes when reading, double vision), or by general symptoms, the most important of which is headache.

Like muscular fatigue, visual fatigue involves several factors:

(a) Ciliary fatigue involves the accommodation muscle which changes the curvature of the lens. Accommodative asthenopia, or deficiency or weakness of accommodation, is seen mostly in people suffering from defects of refraction, especially if these have been overlooked.

(b) Fatigue of convergence causes disturbance of the equilibrium of the extrinsic eye-muscles which control the co-ordinated movements of the two eyes. The visual axes must converge on the object that is being looked at in whatever direction the eyes may be turned.[5]

But general fatigue, even when it is not due to intense use of the eyes, may have an effect on the extrinsic eye-muscles. Measurement of the 'near-point' of accommodation or of the failure to correct latent heterophoria is then a useful measure of general fatigue. Ocular fatigue concerns not only the intrinsic and extrinsic muscles: the eye being first and foremost a nervous apparatus for the detection of light, the retina and the nervous centres of vision are also susceptible to fatigue. The occurrence of variation in the power to fuse rapidly repeated luminous stimuli has given rise to the 'flicker' test for visual and general fatigue, but this is not as reliable as the others previously referred to.

*Auditory fatigue* has two equally interesting aspects:

1. A specific aspect which comprises several factors: adaptation—a general neurophysiological phenomenon that shows itself as a raising of the auditory threshold caused by stimulation, and which disappears when the stimulus ceases—and auditory fatigue, properly

speaking, which follows a stimulus that is either very loud, very prolonged, or very high-pitched, is shown by a raising of the threshold which may be quite considerable and last for some time.[6]

2. A non-specific aspect which is concerned with the integration of the auditory function in psychological and autonomic life. Hearing is a sense concerned with alertness. It stimulates vigilance and affectivity, and stimulates the production of the hormones which produces changes throughout the hormonal and metabolic functions of the organism.

## *Nervous fatigue and fatigue as a general phenomenon*

We have seen how fatigue has diffuse central effects which blur the distinction between peripheral fatigue and general fatigue involving the central nervous system and mechanisms of adaptation. The phrase *fatigue is a general phenomenon* may well be emphasized. This is true in the case of local muscular effort which sets certain formations of the mid- and hind-brain in action, notably the reticular formation. This latter is involved in the sending of motor impulses to the respiratory muscles and those of the face and tongue. It is also concerned with secondary effects on numerous autonomic regulatory mechanisms in the nearby diencephalon. It is activated under the influence of cortical-subcortical reflexes through the medium of adrenalin. The multiple sensory and interoceptive stimuli, and also the affective load, which reveal themselves in the dynamic complex represented by man faced with the problems of his work and his environment, have even greater repercussions[7].

There is also a general biochemical syndrome of fatigue which is really that of a state following adverse conditions. It has several contrasting aspects:

(a) The specific effects are associated with the particular form of adverse conditions concerned. Muscular effort is accompanied by biochemical changes which are not merely local, but which affect the internal environment, for instance, the level of sugar in the blood, the amount of lactic acid, and concentrations of ions and cellular elements of the blood, all of which are related directly and specifically to muscular effort.

(b) The non-specific effects appear later and tend to modify the earlier ones.[8]

This 'second line' of non-specific responses which follows the immediate response of the autonomic nervous system shows the essential role played by the adrenal cortex in fatigue. Measurements of hormone level seem to us among the most interesting of the objective tests of fatigue, for they give an overall measurement of the resistance of the individual.

Effort is a genuine alarm reaction; both the pituitary and the adrenal cortex increase their hormonal output. This is reflected in the increased excretion of corticosteroids in the urine. At the same time, a mobilization of the carbohydrate substrates is backed up by a process of 'neo-glycogenesis' which uses the remnants of amino acids derived from the breakdown of proteins to provide further sources of energy.

In fatigue and over-exertion the hormonal picture is reversed, the more so if not enough food is eaten. The urinary corticosteroids are lowered, simulating a temporary adrenal insufficiency. This temporary exhaustion added to other local and general factors produces the limitation of effort that characterizes fatigue.

In pathological fatigue, prolonged states of asthenia are marked by a measurable degree of hormonal and metabolic depression and are an expression of genuine endocrinal-metabolic exhaustion.

Starting from muscular fatigue, we have finally reached a wider conception of fatigue. It is an overall effect that exerts itself on both the mind and the body of a person subjected to the repeated and multiple conflicts of everyday life. In some way it resembles shock, an acute response to aggression. Both fatigue and shock show the same progressive stages. Alarm represents the physiological response, as seen in the sportsman or the fighter. The precarious stage of adaptation shades into chronic fatigue and exhaustion. This is seen in certain states called 'industrial fatigue'. There is also exhaustion, either the acute exhaustion of the climber or the soldier, or the chronic exhaustion of the former inmate of a concentration camp, merging into pathological states, predominantly asthenic (with certain chronic adrenal or pituitary deficiencies and chronic states of asthenia, reactive or otherwise).

The physiological and biochemical study of muscular fatigue has shown us where the 'bottlenecks' occur, which limit activity. But fatigue is also a general phenomenon that has its place among the major organic and psychological needs of mankind. It therefore tends to lead to a general reduction of activity, not just in certain systems but also in the psycho-physical personality as a whole.

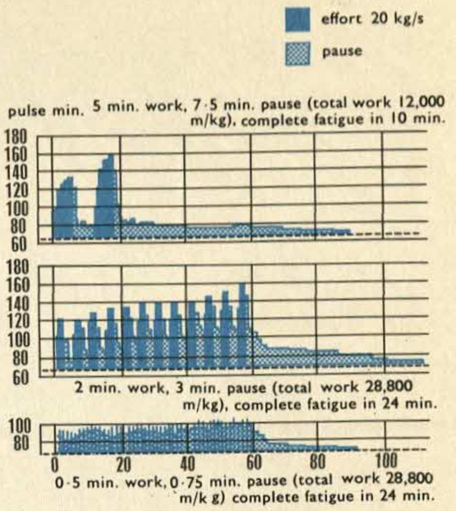


*Fig. 3. Effort of maximum degree (28,800 m/kg) is carried out without fatigue when the alternating rhythm of work and rest is optimum (half a minute of effort followed by three-quarters of a minute's rest). On the other hand, exhaustion is reached in ten minutes with less work (12,000 m/kg) when the alternation of work and rest is less satisfactory.*

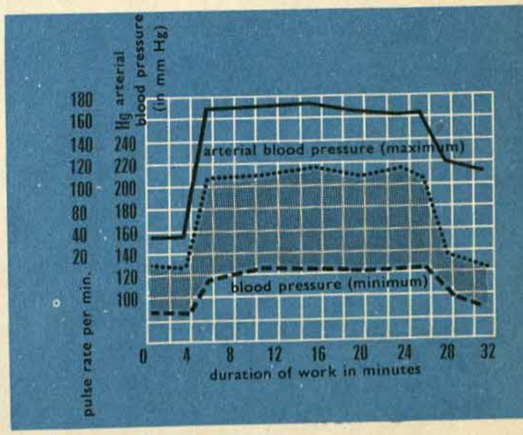


*Fig. 4. Variations in the pulse rate and arterial blood pressure during work. (After A. Eldahl).*

# Extreme conditions

*Jean MALMÉJAC*

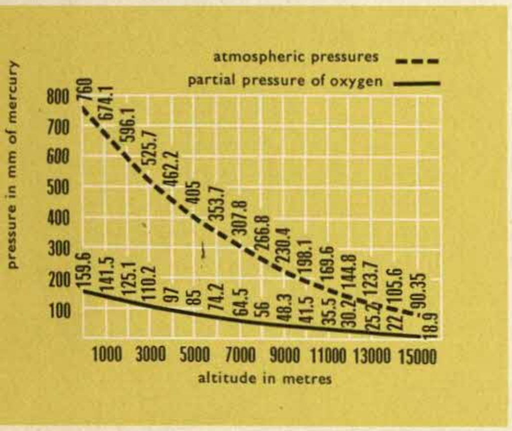


*Fig. 1. Variation of the atmospheric pressure as a function of altitude and temperature between 0 and 15,000 m.*

There are two fundamental principles involved in homoeothermy:

1. The human body is made up of billions of cells which can live (ie, respire, undergo ceaseless physico-chemical changes, and multiply) only under certain strictly determined conditions. In the words of Claude Bernard, these cells live in an internal environment consisting of a watery solution from which they extract what is necessary for their activity and into which they shed the waste materials which result from it. This environment is kept constantly on the move by the circulation, renewed by materials coming from the lungs and the intestines and purified by the cleansing organs, notably the kidney. As long as the equilibrium of the internal environment is kept constant, the organism is capable of survival.

2. Complex regulatory mechanisms which work with great precision keep the internal environment constant. All the major functions of the body, which are called into play by the very disorder for which they have to compensate, participate in the maintenance of conditions favourable for cellular activity, in spite of continual variations both in the tissue activity itself and in the external conditions.

Nevertheless, the efficiency of these mechanisms has its limits. If these limits are passed, the constancy of the internal environment is increasingly threatened, and cellular activity becomes affected. Beyond a certain point, the regulatory mechanisms fail and the individual's life is threatened. In this chapter we shall deal with two types of adverse conditions: changes in the barometric pressure, and changes in temperature.

## Changes in pressure

Man is accustomed to living under a pressure of 760 mm of mercury. He takes his respiratory requirements from the air, which consists of approximately 80 per cent nitrogen and 20 per cent oxygen. When the barometric pressure falls, as happens at high altitudes, the partial pressure of the oxygen falls in proportion. The respiratory exchanges in the lungs are determined by the difference between the pressure in the air in the alveoli and that in the venous blood, and so the exchanges are reduced. Thus the blood no longer becomes sufficiently oxygenated during its passage through the lung and there arises a state of hypoxia, which can be called the chemical effect of the fall in pressure. The organism immediately puts into action various defence mechanisms, and a compensatory pulmonary hyperventilation ensues, but with only limited effects. Observations have been made on high mountains and in laboratories with the help of pressure chambers in which the atmospheric pressure can be varied. These observations show clearly that above a height of 2,500 to 3,000 m (8,000 to 9,500 ft), the tissues of a young person in good health begin to suffer from lack of oxygen. In older people, and even more in those with pulmonary or cardiac trouble, this threshold is lower.

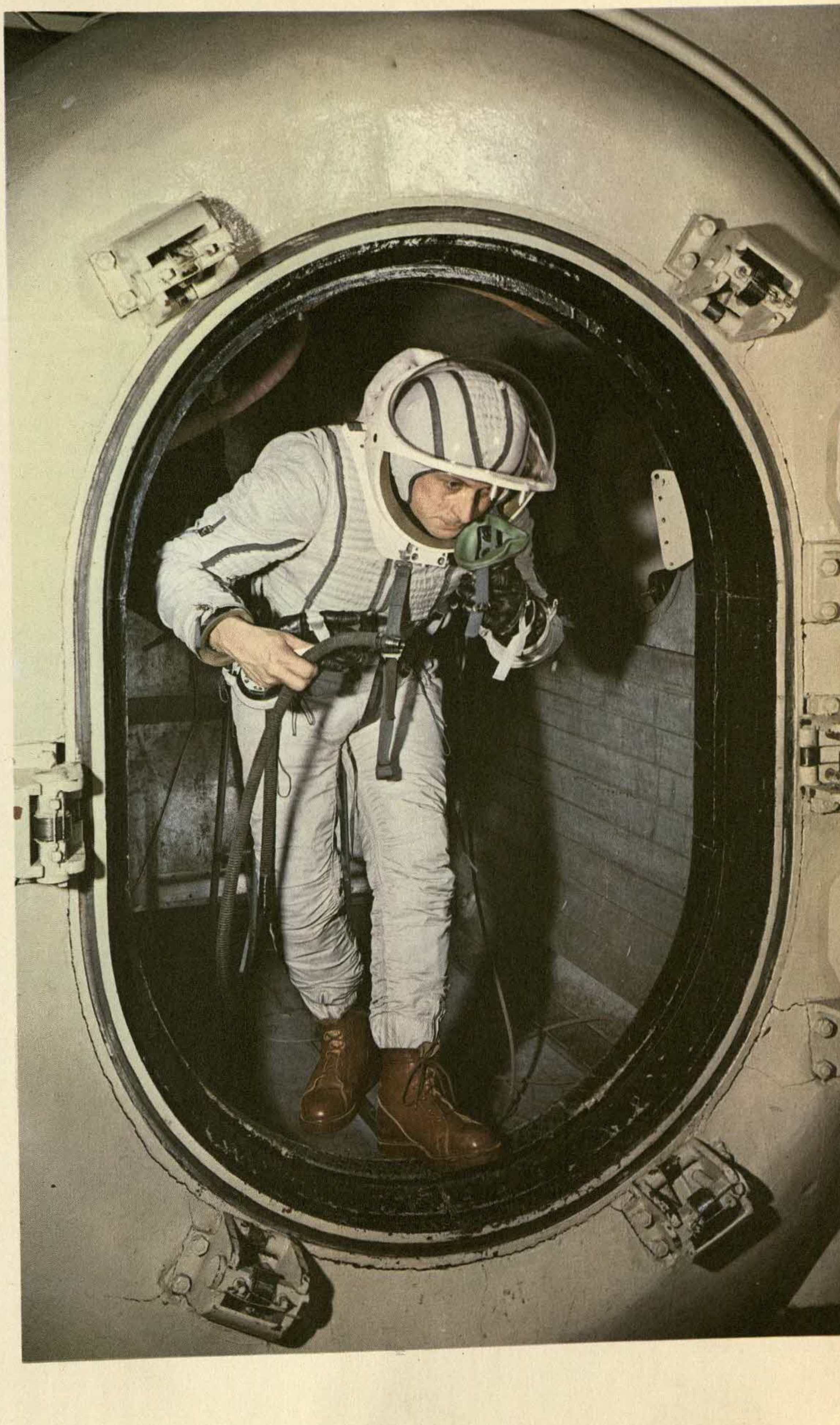
Experimental analyses of the tissue effects show the diversity and complexity of these failures. Most of these effects are not apparent to the anoxaemic person as long as he does not have to make vigorous muscular efforts. Nervous and psychic changes then dominate the scene. At about 3,000 m (10,000 ft) a phase of cortical hyperexcitability occurs. Though not very obvious in man, it can easily be observed in the dog or the monkey through conditioned reflexes or training. At higher altitudes errors of judgment become more and more frequent. It becomes impossible to make mental calculations and the reaction time becomes longer. At about 7,000 to 8,000 m (22,000 to 25,000 ft), loss of consciousness may supervene. The effect is dramatic. The individual loses all contact with the external world, but regains it at once if oxygen is administered. He will remember absolutely nothing of the period of 'anoxic faint'.

In order to protect the organism against the chemical effects of lowering of the

*Man is used to living at a constant pressure (see p. 148). But because of his internal regulatory mechanisms, he can adapt himself to conditions of pressure and temperature which are very different.*

*Below: research on a system of closed-circuit respiration. The study of the adsorption of carbon dioxide and water vapour from the expired gas.*

*Right: a man emerging from an experimental chamber in which it is possible to produce a considerable vacuum, for example, 7 millibars, corresponding to 109,000 ft altitude with 'climbing speeds' reaching 363 ft per second and a range of extreme temperatures from −74°C to 60°C. He has just been testing a space-suit, a made-to-measure air-conditioned air-tight cover which protects him against the fatal effects of very high altitudes. (Photo Lod, taken at the Flight Tests Centre at Brétigny-sur-Orge).*



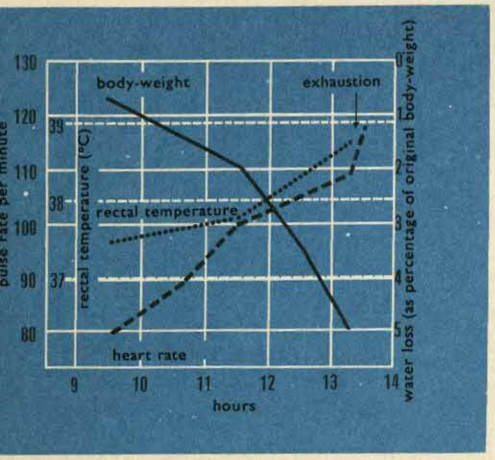


*Fig. 2. Dehydration through perspiration. The syndrome of exhaustion from dehydration in a man in the desert undergoing physical effort for four hours without drinking (highest air temperature, 41°C; after A. H. Brown).*

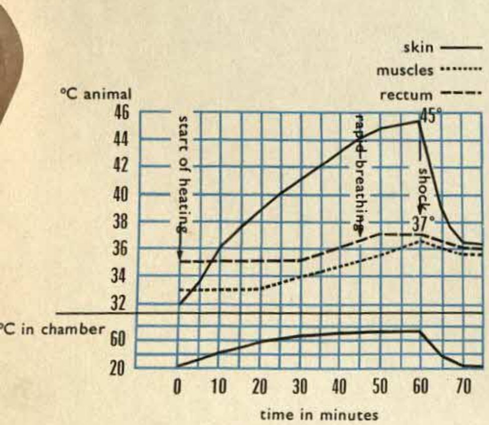


*Fig. 3. Generalized effects of shock in a dog when the skin alone is submitted to a raised temperature of 45°C.*

barometric pressure (eg, in an aeroplane), it is necessary, above 3,000 m (10,000 ft), to inhale oxygen. This threshold has been fixed experimentally, bearing in mind the manifestations of anoxia already described and those which are started indirectly; for example, the resulting pulmonary ventilation will lead to excessive loss of carbon dioxide and will produce alkalosis.[1]

It is for these different reasons that oxygen masks for flyers provide them, above 3,000 m (10,000 ft), with oxygen in quantities strictly determined in terms of the altitude. At 8,000 to 9,000 m (25,000 to 28,000 ft) pure oxygen is supplied. The proper functioning of these masks is frequently checked, for failure at a high altitude is a very serious matter. The 'reserve of time' during which the flyer can still take action is very short; at 12,000 m (40,000 ft) loss of consciousness will come on in about thirty seconds. Incidentally, it would be a mistake to think that the supply of oxygen enables the flyer to go as high as he likes. Taking into account the barometric pressure which exists at 12,000 m (40,000 ft) and at which pure oxygen is inhaled, a flyer is in fact in the same position as one at 3,000 m (10,000 ft) without oxygen, ie, at the limit of anoxaemia. To go above 12,000 m (40,000 ft) it is necessary for the flyer to be completely isolated from the external environment. This is what happens in the pressurized cabins of commercial aircraft, in which one can travel in comfort and security at 12,000 m (40,000 ft), but without pressurization, life would be impossible at such an altitude (fig. 1).

There is also a second factor which makes this isolation from the external environment essential; namely, the physical effects of the lowering of the barometric pressure. Some of these effects are relatively harmless. They are due to the expansion of gas when the pressure is lowered, and are associated mainly with the ears. Pain and a sensation of deafness may occur, which are quickly relieved by a simple swallowing movement or by yawning widely in order to open the Eustachian tubes and so equalize the pressure on each side of the ear-drums. If there is a complete blockage of the communication between the middle-ear and the naso-pharynx, a rapid descent may lead to rupture of the ear-drums, but this seldom occurs.

These mishaps, resulting from too swift a descent, are also well known to divers and aqualung fishermen. Each descent of 10 m (approximately 32 ft) below the surface of the sea corresponds to an increase of pressure by one atmosphere. Equilibrium of the pressures on each side of the ear-drums must therefore be re-established both during the descent and on the return to the surface.

But much more serious accidents may befall a man at high altitudes, or a diver returning quickly to the surface.

If the human organism is subjected to an abrupt decompression, ie, reduction of atmospheric pressure, gas will come out of solution. Nitrogen, an inert gas, is the most important in this respect and at atmospheric pressure at sea level a man weighing 70 kg (eleven stone) will contain 1,000 cc of nitrogen in solution. When the pressure is rapidly reduced, this gas tends to come out of solution and the free gas may appear as bubbles in many different parts of the body. The disturbances which result from this, caused by physical changes, may take different forms, according to where the gas is. Among the most frequent minor forms are pains in the joints or on the course of the nerves, and sensations of itching, with cutaneous reddening. Unfortunately, when the central nervous system, the pulmonary circulation, or the coronary arteries are affected, these disturbances are more serious and may prove fatal.

Such a release of gas from solution may occur at a height of 8,000 to 9,000 m (25,000 to 28,000 ft). In fact, a preventive inhalation of pure oxygen, which leads to the removal of much of the nitrogen, will reduce, again relatively, the incidence of such air embolism. However, it is the isolation of man from the external environment which affords the best protection against both the chemical and physical effects of the lowering of barometric pressure. This isolation is of course essential for flights into the stratosphere and outer space.

Divers have the same problem. The human body can endure pressures of several atmospheres, but the higher the pressure, the more gas will be dissolved. Even oxygen itself can then become harmful in excess. Mental disturbances with hallucinations have been described under pressures of 8-10 atmospheres. But once again, it is nitrogen which is the most important. It dissolves in the body on average at about 1,000 cc for each atmosphere of pressure. After a fairly prolonged stay at high pressure (the dissolving is gradual), the quantities of nitrogen dissolved may be considerable. When the diver returns to the surface, thus undergoing decompression, there is considerable risk of air embolisms being produced. The physical mechanisms and the physiological and pathological aspects are the same for a man adapted to normal pressure who ascends in the air to regions of lower pressure as for a man adapted to high pressures who returns to regions of normal pressure. Each time the pressure is reduced rapidly by half, whether it be from 6 to 3 atmospheres, or from 4 to 2, or from 2 to 1, or from 1 to ½, or from ½ to ¼, the risk of air embolism is present.

We can thus understand why, on the basis of these data, the work of deep-sea divers and of tunnel workers is rigorously regulated. The decompression must be sufficiently slow for the removal through the lungs of the excess nitrogen which has been dissolved, calculated from the pressures experienced and the duration of the stay at a depth. This determines the different levels at which stops are made during the return to the surface, which can amount to several hours, if the excess of pressure has been considerable and fairly prolonged. There are also tables which lay down precisely the length of time to be spent at each level during the ascent.

It is important to understand that from the biological point of view the studies concerning flyers and astronauts are exactly similar to those based on observations concerning divers and tunnel workers. The problems set by the decompression of the flyer who rises above sea level are the same as those of the diver who rises to it from the depths; they obey the same physical laws and give rise to the same type of accidents.

## *Abnormal temperatures*

Variations in the external temperature set in motion physiological corrective mechanisms which act both on the production of heat and on its loss by the body. In the cells, important chemical reactions are continually taking place. This activity is accompanied by a liberation of energy, and part of this appears as heat. It is a commonplace that physical exercise is a source of heat production, but this applies to all types of cellular activity. Even at rest, the human body loses about 2,000 calories every twenty-four hours. This is the 'central heating' which enables man to maintain a body temperature generally above that of his surroundings. The loss of heat, except that lost in respiration (expired air is warmer than inspired and is saturated with water vapour) occurs from the skin by radiation, by convection, or through the evaporation of water.

When threatened by an excessive rise in temperature, the homœothermic subject reduces the production of heat as much as possible (which is relatively little), and increases heat loss by a cutaneous vasodilation and especially, if the surrounding temperature is raised, through perspiration (fig. 2).

A man weighing 70 kg (eleven stone) can thus lose from 1 to 3 litres of perspiration in one hour, and the evaporation of this represents the loss of several thousand calories—a considerable amount. It can thus be seen that conditions which reduce perspiration (as, for instance, scleroderma) or which reduce the evaporation of water from the surface of the skin (as does a humid atmosphere) will obstruct the loss of excess heat. In animals which cannot perspire, such as the dog, this evaporation is brought about by the lungs, and the pulmonary ventilation is considerably raised. The respiratory movements are small and very rapid (up to 200 to 300 per minute) and the dog keeps its mouth open with its tongue hanging out.

In practice, heavy perspiration corresponds to complex inter-changes of water between the blood, the interstitial spaces, and the tissues. If it is prolonged, it leads to a real dehydration. In the desert in summer a man can lose 10 to 12 litres of water a day. Such losses must be made good by the drinking of at least the same quantity of water. However, experience has shown that water alone is not sufficient to re-establish equilibrium; salt must also be taken. Perspiration is rich in salt, and if the loss of salt is not made up, water that is drunk is rapidly wasted (mostly by perspiration, which is increased by drinking) without any rehydration of the tissues occurring. The effect is even worse because more salt is lost. It is well established now that the ingestion of suitable quantities of salt is absolutely necessary for tissue rehydration. The weakness which accompanies heavy perspiring disappears only if both salt and water are supplied to the body (fig. 3).

The part played by the skin is most important in combating heat. It may be useful to mention here the dangers of excessive sunbathing. The sunburn so often seen on the beach, where the desire to become brown makes one forget the inconveniences of trying to do so, is a true burn which can even produce blisters. The skin under the influence of infra-red and ultra-violet rays reacts by vascular and even by physico-chemical

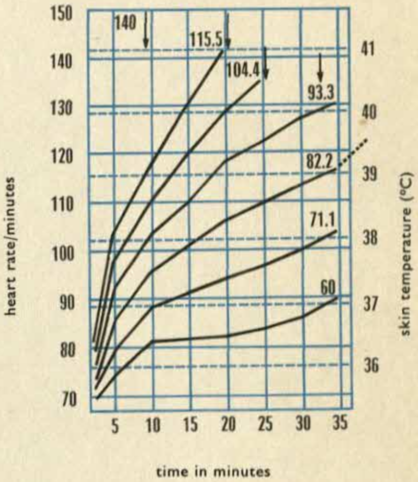


*Fig. 4. The limits of resistance of man to high temperatures.*

(1) Alkalosis: *a rise in the alkali reserve of the blood.*

# *Abnormal temperatures and pressures*

*To measure the limits of human resistance, volunteers undergo certain experiments in the course of which pressure and temperature vary violently. Below: a study of the effects of low pressures. A pilot is subjected to conditions identical with those found at great altitudes. Bottom: a study of the thermo-regulation of a rat subjected to different temperatures. One can measure its heat production and oxygen consumption. (Photo Lod, taken at the Research and Study Centre for Aeronautic Medicine, Paris).*

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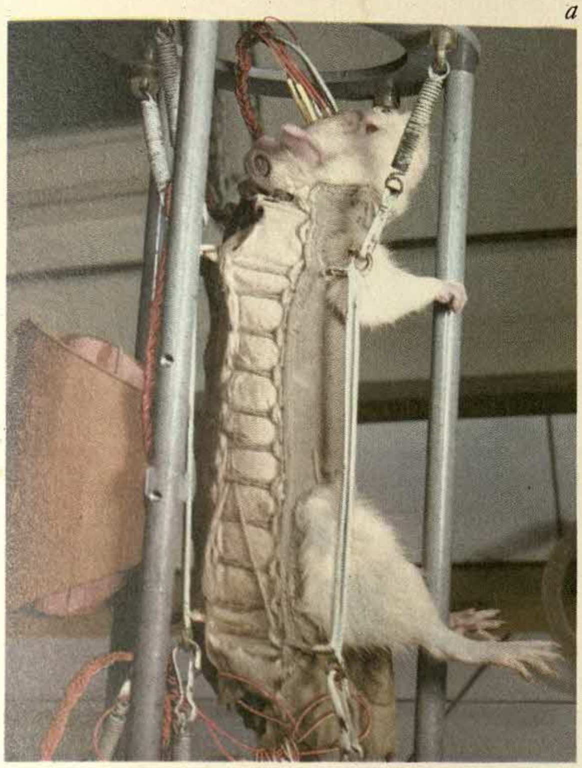

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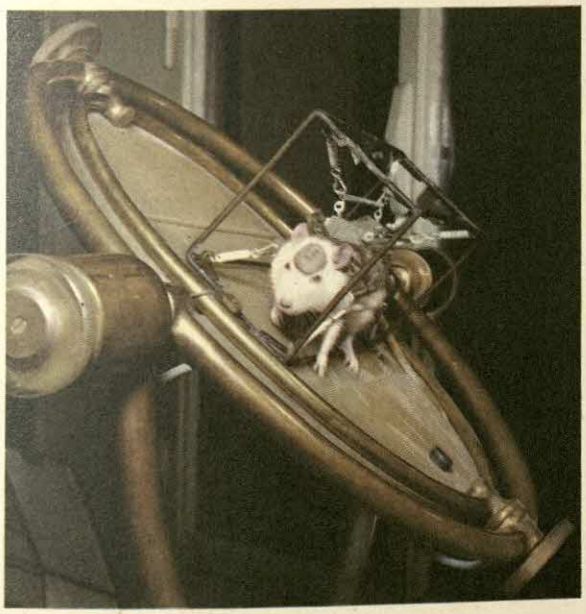

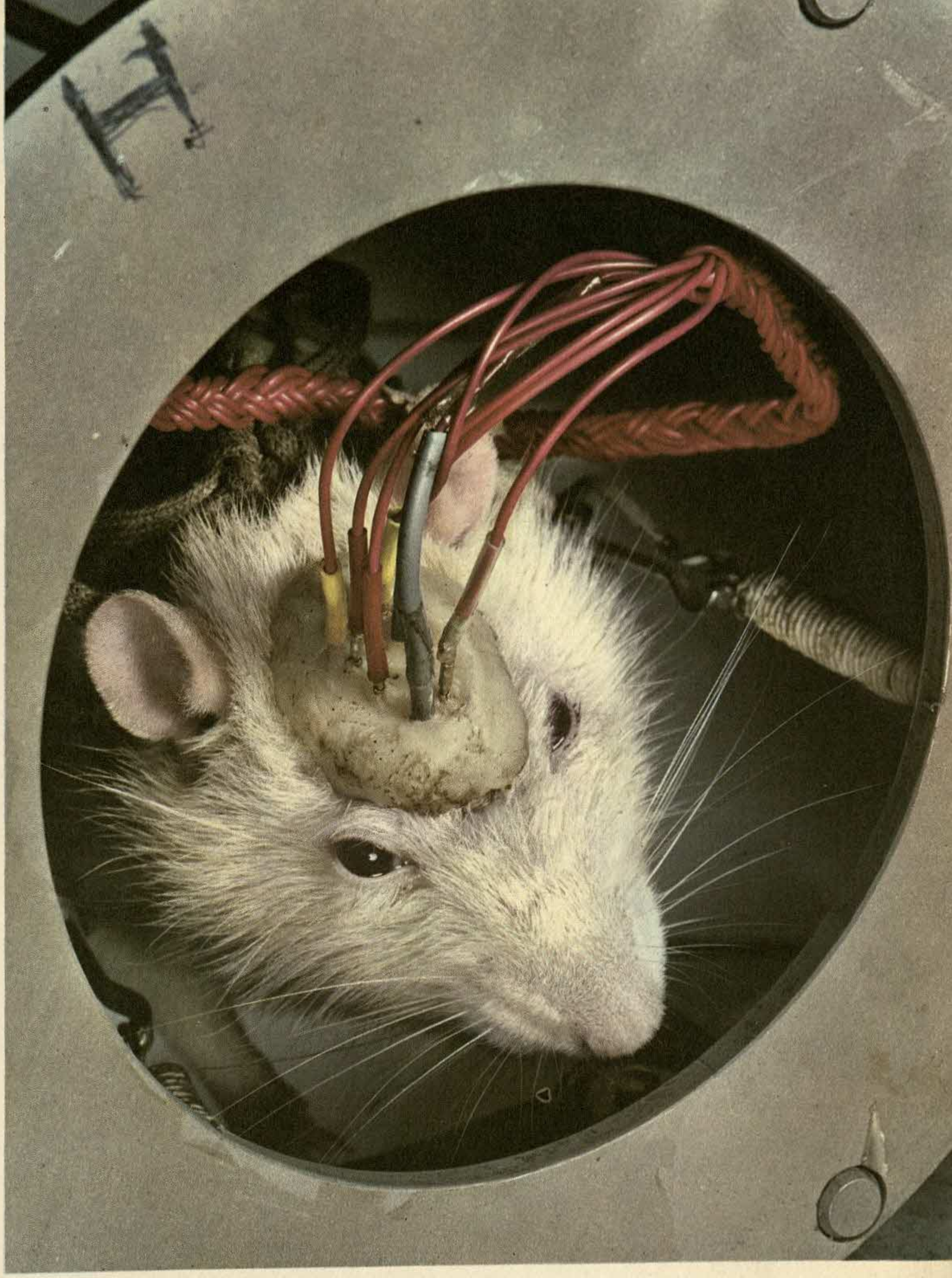

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*The preparation of a rat for a voyage in space. Animals were sent into space before man undertook such voyages; their reactions were carefully studied on the ground before they were sent up in rockets. (a) shows a rat in its special space suit and with the suspension system used for rocket travel. The springs serve to lessen the accelerations to which the rat is subjected; (b) shows the apparatus as a whole. In (c) the rat is trained to face the accelerations before it is put into the rocket; (d) shows the rat in its space cabin. Electrodes have been placed and will remain permanently in various parts of the brain to register the electrical activity of these parts (indicating sleep, waking, etc). An animal that has been operated on under aseptic conditions and is in perfect health can be used for long-term experiments. Its general condition is physiologically almost normal and enables one to note the normal behaviour of such animals under different conditions. (Photo Lod, Research and Study Centre for Aeronautic Medicine, Paris).*

changes. The latter may have far-reaching effects and lead to more serious reactions that extend well beyond the simple skin effects. This point cannot be over-emphasized, nor can the wisdom of exposing the skin to the sun only gradually. The protection of the skin by the wearing of ample but light clothing is very important in hot countries.

Experience shows that even in dry climates the organism can endure very high external temperatures only for very short periods. If the body's defences are overwhelmed by a high temperature and the internal temperature increases, heatstroke results. The organism stands hyperthermy badly. The margin of internal temperature variations is a very narrow one in this case: 44°C to 45°C (110°F to 113°F) represents the upper extreme of temperature compatible with life.

The limits are much greater when it comes to lowering the temperature. A man exposed to cold reduces his heat loss (cutaneous vaso-constriction) and increases his heat production. The cellular combustion is raised through the influence of nervous and endocrine regulatory mechanisms and through muscular exercise. Shivering is only a reflex form of this exercise. However, the efficiency of these mechanisms has its limits. In a person exposed to very low temperatures certain parts of the body become vulnerable; for instance, the feet and hands. Cold leads to localized vasodilator reactions, of which chilblains are a first indication. If the action of cold is too intense, serious circulatory troubles will follow and will lead to gangrene. The internal temperature is safeguarded for the time being, but the most exposed parts of the body are sacrificed. Clothing plays the part of an insulator. It can be adapted to the temperatures expected and, if necessary, heated, as in flying suits. These give protection to the wearer even at temperatures of −40°C to −50°C (fig. 4).

When a man is exposed to low temperatures without sufficient protection, his thermoregulatory system runs the risk of breaking down. The struggle against cold is lost and the internal temperature begins to fall; this is called hypothermy. The main functions of the body progressively slow down. Below 30°C (86°F) consciousness is lost. Then the circulation slows down, while the respiratory movements diminish in amplitude. If no help is forthcoming, death supervenes, usually between 25°C and 20°C (77°F and 68°F). However, in medical literature it is possible to find certain exceptional cases of persons whose internal temperature has fallen to about 20°C (68°F) and who nevertheless have been resuscitated. Death from cold involves, in fact, a general 'bogging down' of all the main functions of the body. Experience shows that in warm-blooded animals that have been cooled to 20°C (68°F), all the tissues are in a state of 'slow motion'. The cellular activity is reduced and failure of nervous action dominates the picture, leading to failure of the important functions, particularly respiration.[2] Experience has shown, however, that by the use of artificial respiration it is possible for very low temperatures to be reached.

It is on the basis of these findings that it is possible today to use 'controlled hypothermy' during surgical operations, such as those on the heart, which entail prolonged arrest of the circulation. This arrest is well supported at low temperatures. While at normal temperatures an arrest of the cerebral circulation for three or four minutes causes grave secondary damage, such an arrest can be continued for thirty-five to forty minutes at a temperature of 16°C to 18°C (60·8°F to 64·4°F). Experiments on dogs, making use of the conditioned salivary reflex, and on monkeys trained to perform various actions, have demonstrated this. Observations made recently on human beings during operations on the heart under hypothermy (using an extracorporeal circulation) have also confirmed these results.

The study of hypothermy, its effects, and the way in which disturbances are produced has thus enabled us to use low-temperature techniques in connection with surgery. In medical therapy, chilling, under the debatable name of 'hibernation', involves a drop of temperature of only 2°C or 3°C; this is generally brought about by the use of various chemical products which reduce the activity of the normal thermo-regulatory mechanisms.

This brief account shows clearly that man, who is adapted to a precisely determined external environment, cannot be removed from it without running risks. His resistance is limited and protection is necessary. This is true of the variations in barometric pressure and in temperature which have been discussed. These two types of adverse conditions, however, constitute only one example, among many, of the sort of question which modern technical developments set the biologist. Many research workers, specialists in various fields, are concerned with these matters and are thus contributing indirectly to facilitate man's adaptation to new conditions of life.

(2) *Isolated tissues which have been frozen can regain their functional activities after being re-heated. In the case of the whole organism, the problems are more complex, for the maintenance of one of the principal functions, such as respiration, requires the intervention of complex nervous co-ordinations which are not easily deranged.*

# Correlations between organs

### *Pierre VENDRYÈS*

*The functioning of each organ in the same organism cannot be properly understood in isolation: the organism must be considered as a whole because the various organs work together; the activity of each one assumes its full significance only in relation to that of the others and to the organism as a whole. These functional correlations are shown in various ways.*

It is significant that in presenting the physiology of the organism, it is necessary to consider it on two different planes, shown as a double-entry table. In the vertical columns the various organs are placed beside each other. In each column we write down the various activities of these organs. For example, in the column for the liver we indicate its role in the metabolism of carbohydrates and its role in the metabolism of proteins; in the column for the kidney, we put down its various activities in the elimination of water, sodium, and urea. In this analytical form the various organs are represented individually.

If we now write down horizontally the various types of metabolism, we shall find that the organs which take part in one particular type of metabolism appear next to each other. For example, on the line for the metabolism of glucose will be digestive organs which break up the carbohydrates, the liver which stores up glucose, the pancreas which secretes the insulin regulating the blood sugar, the muscles which use glucose, and the kidney which eliminates the excess glucose. This second method of treating physiology, more synthetic than the first, shows us that the various organs are functionally correlated. For example, the storage of glucose in the liver and the use of glucose by the muscles are functionally connected.[1]

## *Correlations of organs and of the internal media*

About a century ago, Claude Bernard (1813-1878) showed the existence and physiological importance of the internal environment of the organism. These are liquid media that circulate and contain in watery solution all the substances needed by the cells.

One of these media, the arterial blood,

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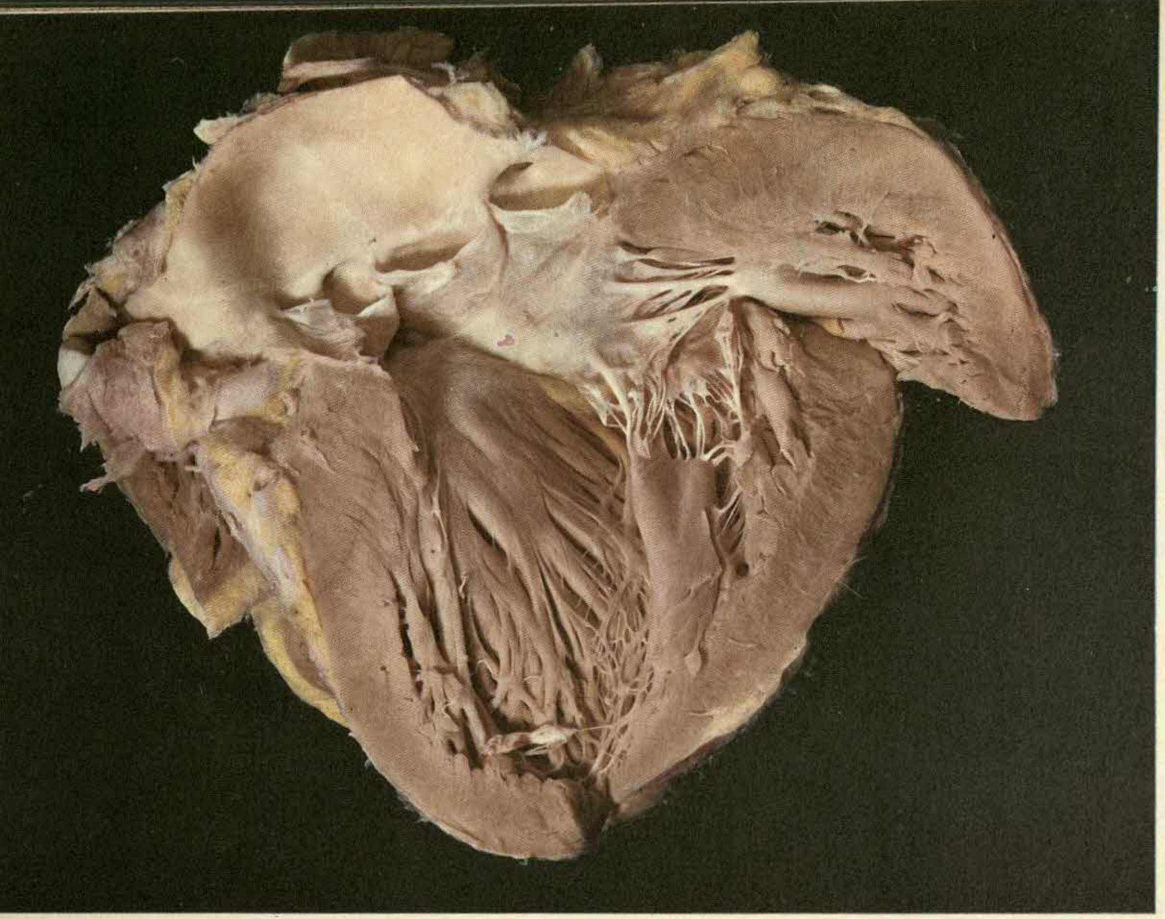
(1) *These correlations are often effected by a chemical agent. Thus certain organs act from a distance on the functions of other organs by means of hormones.*

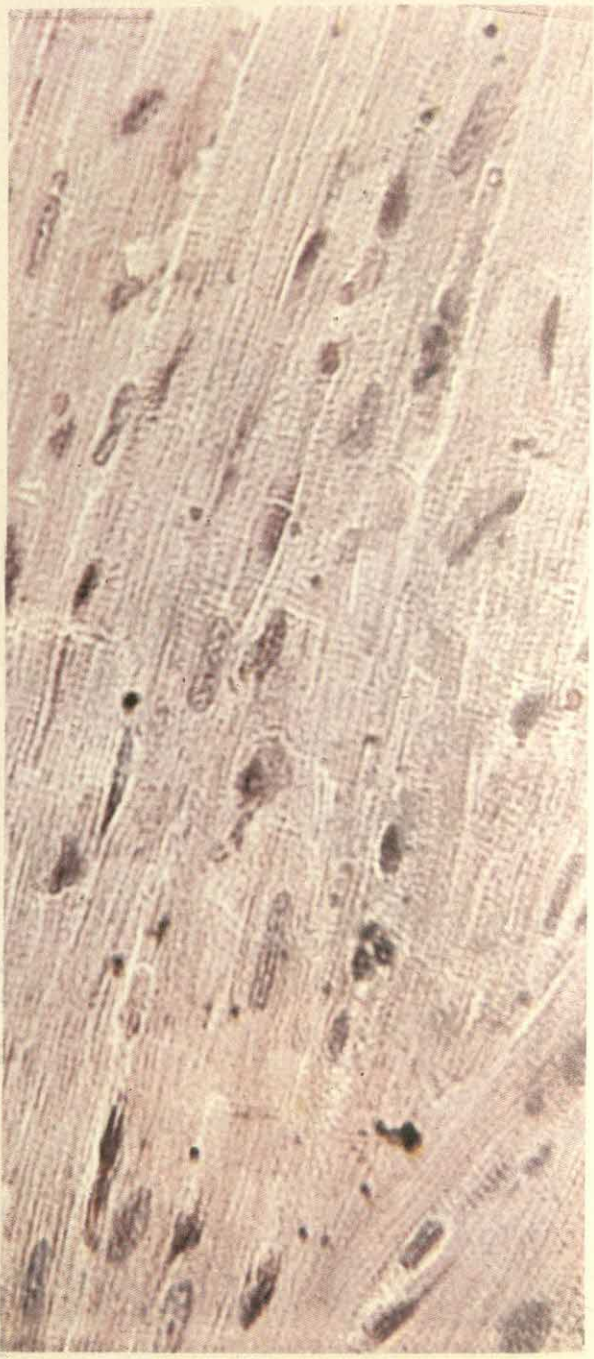
(2) *Cannon has called this concept 'homeostasis'.*

(3) *Anatomically, the autonomic centres are situated in the interior of the central nervous system. From the lower extremity of the spinal cord up to the diencephalon, these centres are grouped round the central canal as far as the third ventricle, between the centres concerned with movement and those concerned with sensation.*

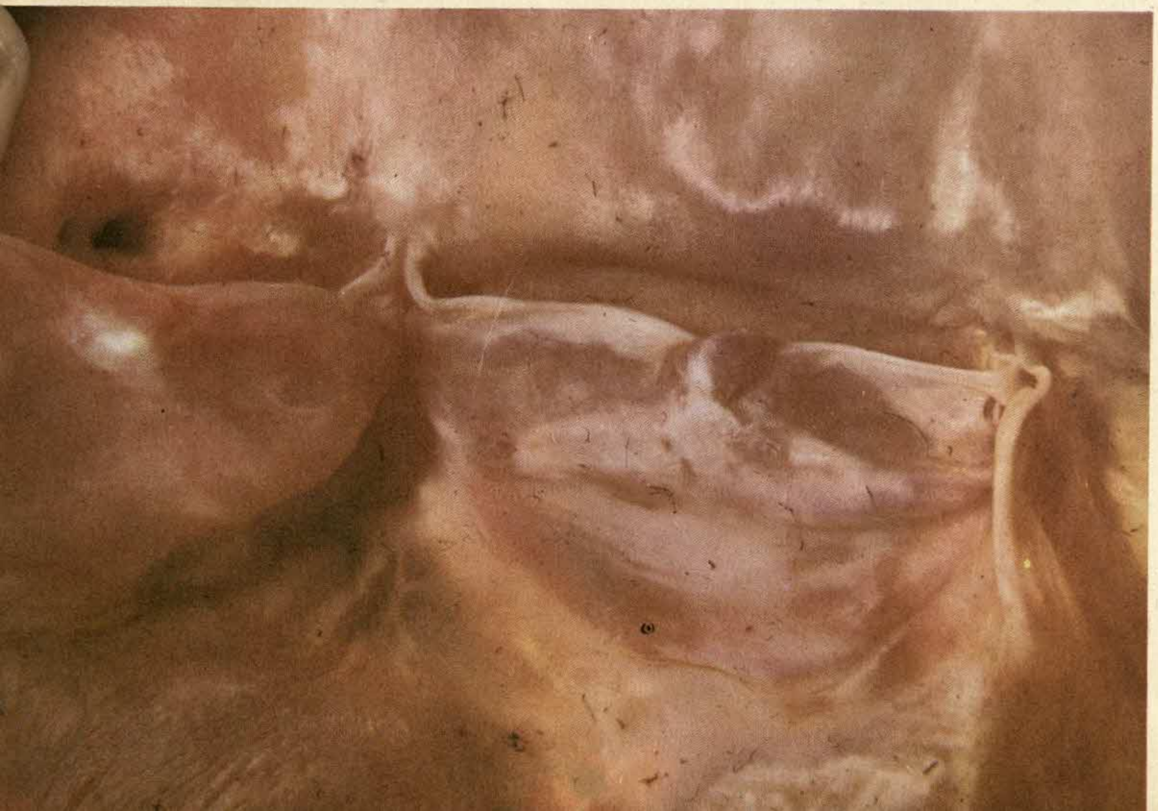
(4) *The most celebrated of these machines are the 'artificial animals' constructed by Grey Walter, and W. R. Ashby's homeostat. With the aid of these models it should be possible to understand better the correlations which exist between the various centres inside the nervous system itself. The science of cybernetics, as Norbert Wiener termed it in 1947, attempts in even bolder fashion to deal with these same problems abstractly and mathematically. The derivation of the name cybernetics indicates that it is concerned with control. Cybernetics is the science that deals both with control and information in animals and in machines.*



# *The vital engine*
# *of the organism*



*As Vendryès says, the life of the various organs is the result of multiple correlations. Nevertheless the heart is the essential engine and permanent stopping of its beat means death. It is shown as a whole, above to the left, with the ascending aorta and left ventricle displayed. Below: the valves which prevent the blood from being returned at the systole; that is, the contraction of the heart. Centre: a section of heart muscle. Right-hand page: the remarkable arrangement of cords and papillae attaching the valves to the internal walls of this indefatigable muscle which, from birth to death, contracts about two thousand million times. (Photos Lod, taken in Professor Jean Gosset's Laboratory of Pathological Anatomy, Hôpital Saint-Antoine, Paris).*



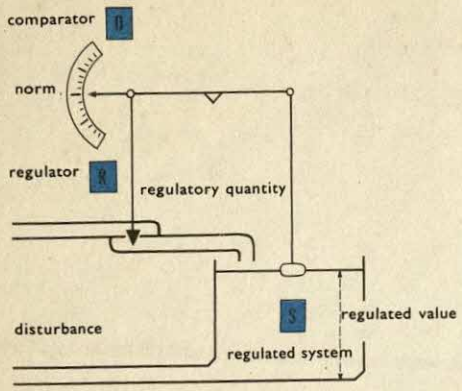


*Fig. 1. Diagram of a water-level regulator.*

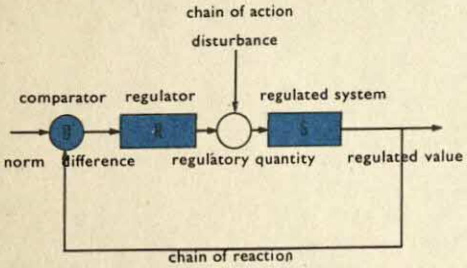


*Fig. 2. Functional diagram of a regulatory system.*

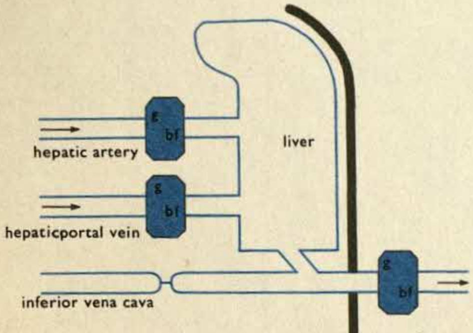


*Fig. 3. Experiment by Soskin on regulation of the blood-sugar level by the liver. The inferior vena cava of a dog is ligatured before it reaches the liver. Then the blood-flow (bf) and the concentration of glucose (g) in the blood are measured in the portal vein, the hepatic artery, and the vena cava. The experiment consists of increasing the concentration of glucose in the blood and of measuring the variations in the outflow of glucose from the liver in terms of the variations in the concentration of glucose in the blood.*

is common to all the cells of the organism and thus is one of the factors that make for the unity of the organism. At the same time, this arterial blood is a product of organic synthesis. The organs exercise a double influence on the blood: they are responsible for its composition and they also maintain this composition at a constant level. In Claude Bernard's own words, 'All actions, however varied, have but one object: to preserve the constancy of the conditions of life in the internal environment'.[2]

It is apparent, then, that the functioning of the organs is determined not only by the relation between them, but to an even greater extent by the medium formed by the blood. Arterial blood appears as the functional link between very different organs. Under the term 'Bernardian physiology' should be grouped the activities of all the organs whose functions are related to the arterial blood. These organs include the digestive organs, the liver, the lungs, the kidneys, the circulatory organs, the glands of internal secretion, and the autonomic nervous system. The constancy of the physico-chemical conditions of the blood is maintained by the organs through regulation. But the organs function in relation to these physico-chemical conditions, the constancy of which they maintain.

## Theoretical physiology

It is now possible to carry our understanding of these correlations much further. This is the object of theoretical physiology, an emerging branch of science which attempts the mathematical analysis of the functional relations within the body.

Theoretical physiology applies to the body's regulatory mechanisms the mathematical theory of cybernetics which has been worked out by engineers during the last twenty years. In order to understand this, we must recall the fundamental definitions of this theory of regulation. We can take as a simplified example the regulation of a water level (fig. 1). The tank forming the regulated system (S) contains water and it is the level of this that we wish to regulate. Variations in the level, caused by disturbance, are detected by the float and compared by the comparator (D) with a standard of reference, or norm. The difference between the altered level and this reference level sets off the regulator (R), which changes the rate of inflow into the tank and finally restores the level to normal. The change in the inflow thus acts as the regulator.

Engineers, however, represent their regulatory mechanisms in a more abstract form. The elementary plan of a regulatory mechanism is formed by a regulatory loop which comprises a chain of action and a chain of reaction. The chain of action includes the various systems, the comparator (D), the regulator (R), and the regulated system (S), as well as the various values, the norm, the regulator, the disturbance, and the regulated value (ie, the value to be regulated). The chain of reaction establishes a feed-back relation between the regulated value and the norm, by means of the comparator (D), which measures the difference between the regulated value and the norm (fig. 2).

The mathematical relationship between the regulated value (X) and the regulator (Y) is of great importance. In particular, it is important to distinguish between regulation by proportional action and regulation by integral action:

Regulation by proportional action: $y = kx$.

Regulation by integral action: $y = k\int xdt$.

Theoretical physiology, when it wishes to apply the theory of regulation to its own regulatory activities, must begin by defining its regulatory loops. The fundamental regulated system (S) is the blood. The regulated values are the various constituents of the blood. The regulators (R) are the various organs which keep the composition of the blood constant. They are set in action by the deviations of the actual levels from the blood norms.

In connection with this theoretical physiology, I enunciated in 1958 the following law. The blood is regulated in its composition, ie, in the concentration of its various components, as follows: when the regulator is itself a concentration, there is regulation by proportional action; when, however, the regulator is an output, the regulation is by integral action.

This law explains the mathematical correlation between the functioning of those organs which act as regulators of the blood and this arterial blood (figs. 3 and 4).

## Nervous correlations and sensitivity

Neurophysiology is an important division of physiology additional to that established by Claude Bernard. The correlations between the nerve centres are very complex. A simple way of showing these correlations is by defining the different types of sensitivity through which the nerve centres enter into relation with other centres.

The first correlations that we wish to define are those between the Bernardian physiology and neurophysiology. They can be exhibited by both anatomy and physiology.[3] Physiologically, the correlation between Bernardian physiology and neurophysiology is shown by the existence of an interoceptive sensitivity. The receptor organs for such sensitivity are found in the viscera and the blood vessels. For example, nervous plexuses sensitive to distension and irritation are found in the walls of the intestine, and there is a direct link, brought about mainly by the autonomic nervous system, between the degree of activity of an organ and the intensity of the circulation of blood inside this organ. The circulatory volume varies from one moment to another in each organ, according to variations in its activity.

The functioning of the nerve centres is subjected to a second type of correlation which also has an anatomical and a physiological expression. This has been called, since the time of Sherrington, proprioceptive sensitivity. In this type of sensitivity the nerve centres are linked directly to the organs concerned with the static posture and the dynamic movements of the body. The receptors concerned with this type of sensitivity are situated in the periosteum of the bones, in the capsules and ligaments of the joints, in the tendons of the muscles, and in the interior of the muscles themselves. For example, the stretching of a tendon drags on the Golgi corpuscles within the tendon, and the contraction of a muscle is measured by certain specialized muscular fibres, the neuro-muscular spindles. Proprioceptive sensitivity thus has its own type of receptor organs. This type of sensitivity is closely concerned with the harmonious interaction of muscles, both those concerned with static posture and those involved in dynamic movement. Its action may take effect through simple reflexes. Thus Sherrington and Liddell described the myotactic reflex in which the tension developed in a muscle is increased in a reflex manner as it elongates.

But proprioceptive sensitivity also involves more complex systems. Through the Flechsig and Gowers tracts in the spinal cord, its messages reach the cerebellum, one of the centres concerned with regulation of motor activity. Proprioceptive sensitivity includes also the whole of the vestibular system, the organ which orientates the head and the body in relation to the force of gravity, working through receptor organs, the utricle and the semi-circular canals. It is through this link that the tone of a muscle depends on the position of the head in relation to that of the trunk, or to the vertical, as was shown by Magnus and Klein. This proprioceptive sensitivity reaches into the spinal cord by means of the Goll and Burdach columns and then into the Reil tract in the brain-stem, up to the thalamus, the centre for all types of sensitivity, and from there up to the cerebral cortex. Proprioceptive sensitivity thus establishes a correlation which extends to the whole of the nervous system between the bony skeleton and the muscular systems and the nerve centres.

Through a third type of sensitivity, exteroceptive sensitivity, the nerve centres enter into contact with the outside world. The receptors of this sensitivity are situated in the skin. The nerve endings of some of these, which are concerned with touch and pain, are in the epidermis; the originating corpuscles of others, which are sensitive to changes in temperature, are situated in the dermis; others which respond to pressure are situated deeper in the dermis.

The central nervous system is also kept in touch with the outside world by much more elaborate sensory systems: the cochlear apparatus for hearing, the optical apparatus for sight, and the olfactory apparatus for smell. After being relayed in the thalamic region, the sensory pathways reach certain localized regions of the cerebral cortex.

This problem of correlation has recently been investigated by new methods. In these experiments the idea has been to devise and then construct physical models, making use of mechanics or electro-magnetism or electronics in such a way that the machines show certain types of 'behaviour' that may be compared with those of animals.[4]

## Autonomy

Thus we arrive finally at the most important of all relationships, that of the organism as a whole with the external environment. From all that has been said so far, we can see that the general behaviour of the organism involves its various organs. Movement, for example, involves the organs of nervous control, the contraction of the muscles, the energy reserves of the liver, and variations in the local circulation.

But the most important characteristic of this behaviour is that it is free in relation to the external environment.

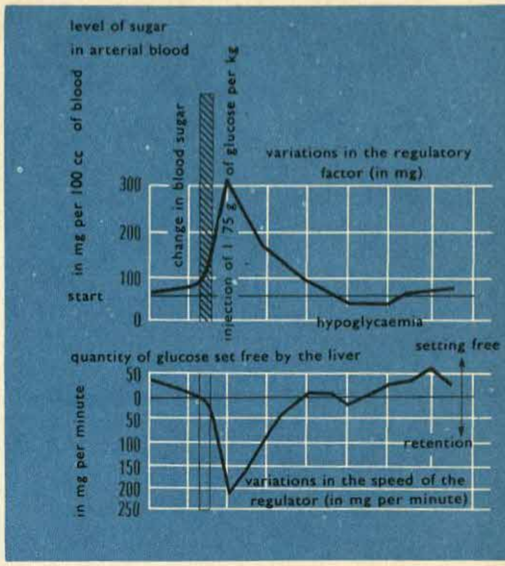


*Fig. 4. The curves which result from the experiment shown in fig. 3. The outflow of glucose from the liver varies as a function of the concentration of glucose in the blood. This variation occurs in the opposite direction to that of the normal level in the blood. One can say that the function of the liver in the regulation of the blood-sugar level is by integral action.*

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